Cholinergic deficiency and inflammation in cognitive dysfunction
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Chapter 5

The association of neuroleptic sensitivity in Dementia with Lewy bodies with a false positive clinical diagnosis of Creutzfeldt-Jakob disease

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A.J.M. Rozemuller-Kwakkel
W.A. van Gool

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ABSTRACT

Dementia with Lewy bodies (DLB) and Creutzfeldt-Jakob disease (CJD) share clinical features like cognitive decline, motor disturbances en psychiatric symptoms. Overlapping symptoms may cause physicians to mistake DLB for CJD.

Clinical data of 12 patients with autopsy-confirmed DLB who had been clinically suspected to suffer from CJD were analysed to investigate possible clinical features which led to misdiagnosis.

There was an association in time between administering neuroleptics and rapid clinical deterioration in 8 out of 9 patients.

It is suggested that the neuroleptic sensitivity in DLB fuelled the misdiagnosis of CJD in the presented series. Diagnostic confusion between CJD and DLB may have important clinical consequences and may lead to treatment restrictions.
INTRODUCTION

There are several reports on patients with autopsy-confirmed dementia with Lewy bodies (DLB) who had been clinically suspected to suffer from Creutzfeldt-Jakob disease (CJD). Overlapping symptoms may cause physicians to mistake DLB for CJD. CJD is characterised by cognitive decline accompanied by focal neurological signs (ataxia, pyramidal/extrapyramidal signs, myoclonus, akinetic mutism) with a rapidly progressive course. In DLB, nowadays considered a common cause of dementia second to Alzheimer’s disease, symptoms accompanying dementia are parkinsonism, a fluctuating course, visual hallucinations and neuroleptic sensitivity. The latter can cause a rapid deterioration in the course of the disease, and this also may lead physicians to consider CJD in the differential diagnosis.

We describe 12 patients with a clinical suspicion of CJD in whom autopsy revealed pathologic lesions characteristic for DLB. The available clinical data were analysed to investigate clinical characteristics which led to the clinical misdiagnosis.

METHODS

Since 1997, patients who are suspected to suffer from Creutzfeldt-Jakob disease in the Netherlands are sent to the University Medical Centre in Utrecht (UMCU) for post-mortem pathological examination. Between 1997-2003, 169 consecutive brains were examined for presence of Creutzfeldt-Jakob pathology. In 77 patients the diagnosis of CJD was pathologically confirmed. Twelve patients had cerebral lesions characteristic for DLB. Other diagnoses were Alzheimer’s disease (41 patients), multiple infarcts, limbic encephalitis, extensive metastasis and metabolic encephalopathy.

Clinical data

All available data including medical records were retrospectively studied after obtaining consent from relatives. Standardized checklists, rating signs and symptoms related with CJD and DLB, were designed according to modified Masters criteria for CJD and McKeith criteria for DLB. Clinical features were categorised in cognitive decline, fluctuations in cognition or consciousness, visual hallucinations, pyramidal symptoms, extra-pyramidal symptoms, cerebellar symptoms and myoclonus. Results of technical investigation (EEG, CT, MRI and CSF) were noted.

Patients were classified both for CJD and DLB according to the international diagnostic criteria.
Medication and neuroleptic sensitivity

All medication was recorded. For each individual drug, we noted dose, exact duration of administering and physical reaction on usage. When patients had used neuroleptics, clinical records were looked for changes in the pattern of symptoms. We considered neuroleptic sensitivity present according to McKeith.7,8

RESULTS

Clinical information was available for all 12 patients. The group consisted of six men and six women (Table 1). Mean age of onset was 71.8 years (range 44-85 yrs.) and mean age of death 75.6 (range 56-87 yrs.). Mean duration of illness was 45.3 months (range 6-148 months).

Clinical presentation

Five patients (41.7%) presented with symptoms of cognitive decline (Table 1). In two, cognitive decline was from the onset of disease accompanied by visual hallucinations. Of these two, one patient presented with extra-pyramidal and pyramidal symptoms as well. Among seven patients (58.3%), extra-pyramidal symptoms were the sole feature of disease at presentation (Table 1).

Ancillary investigations

An electroencephalogram (EEG) was performed once or repeatedly in 11 of the 12 patients. None of these EEG’s showed the typical periodic spike wave com-
plexes as seen in CJD. All EEG’s showed considerable slowing of background rhythm.

Brain imaging was performed in nine of the 12 patients. Four patients underwent a MRI-scan and 5 patients had a CT-scan of the brain. All these scans showed diffuse cortical atrophy. Increased signal intensities in the basal ganglia were not reported, but diffusion weighted and/or fluid attenuated inversion recovery (FLAIR) sequences where not always performed.

Examination of cerebrospinal fluid on the presence of the 14-3-3 protein was only performed in one patient. The Western blot showed a weak band near the spot where usually the band of the 14-3-3 protein is expected. The result of this test was interpreted as “inconclusive”.

**Course of disease**

All twelve patients developed cognitive deterioration at some point in their disease (table 2). Among eight (66.7%) of them, fluctuations in cognition, attention or alertness were reported. Visual hallucinations were found in ten patients (83.3%). Nine patients (75.0%) developed extra-pyramidal symptoms. Extra-pyramidal symptoms were often accompanied by myoclonus (55.5%), pyramidal symptoms (33.3%) or cerebellar symptoms (44.4%). One patient showed myoclonus without presence of other motor disturbances. In retrospect five patients fulfilled the diagnosis of possible CJD based on the international diagnostic criteria (Table 2). The other 7 patients did not meet these criteria due to a disease course of more than 2 years.

**Table 2: Clinical features during course of disease and diagnostic classification**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD</th>
<th>FC</th>
<th>VH</th>
<th>EPS</th>
<th>MC</th>
<th>PS</th>
<th>CBS</th>
<th>Criteria DLB</th>
<th>Criteria CJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
<td></td>
<td>probable</td>
<td>other</td>
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<td>possible</td>
</tr>
<tr>
<td>6</td>
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<td></td>
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<td>other</td>
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<td>probable</td>
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<td>+</td>
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<td></td>
<td></td>
<td></td>
<td>probable</td>
<td>possible</td>
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<td>+</td>
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<td>other</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>probable</td>
<td>other</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>probable</td>
<td>possible</td>
</tr>
</tbody>
</table>

CD=cognitive decline; FC=fluctuating cognition; VH=visual hallucinations; EPS=extra-pyramidal signs; MC=myoclonus; PS=pyramidal signs; CBS=cerebellar signs
Neuroleptic sensitivity

Anti-psychotic use and clinical observations following usage of a particular drug are shown in Table 3. Nine patients received anti-psychotics. Classical anti-psychotics (haloperidol, pipamperon or bromperidol) were administered in three (cases 3, 4, 5). Four patients (cases 2, 7, 10, 12) were given atypical anti-psychotics (clozapine, olanzapine or risperidon) as well. Two patients (cases 8, 9) received exclusively atypical anti-psychotics.

All but one of the nine patients using anti-psychotics (cases 2, 4, 5, 7, 8, 9, 10, 12) showed deterioration of clinical symptoms after starting this medication. In five out of these eight (cases 2, 5, 7, 10, 12), clinical deterioration developed after administering haloperidol, representing all cases using haloperidol within our group of patients. These patients died 18 days to 10 months after haloperidol use was started. Among three patients (cases 7, 10, 12), haloperidol was administered right before, right after or simultaneously with another anti-psychotic drug. In case 7, motor decline developing during combined haloperidol and risperidon use, persisted after ceasing haloperidol and continuation of risperidon. In case 10, clozapine was given before haloperidol was administered. Clozapine was associated with the occurrence of myoclonus and worsening of the overall physical condition. When clozapine was replaced by haloperidol, a clinical picture developed resembling neuroleptic malignant syndrome (NMS). Tachycardia, tachypnea, dehydration, and loss of consciousness were reported. Clozapine was given in case 12 after one day of haloperidol-usage, because swallowing problems emerged. During clozapine usage, the clinical situation worsened rapidly.

Both patients (cases 8, 9) that received olanzapine developed severe deterioration of clinical symptoms. These patients developed visual hallucinations and motor symptoms resulting in severely decreased mobility, after administering olanzapine. Patients died within 2 and 4 months respectively after olanzapine was started.

One patient (case 4) developed reversible worsening of cognitive symptoms, visual hallucinations and extra-pyramidal symptoms after receiving bromperidol.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Psychotropic Drugs</th>
<th>Clinical observations</th>
<th>Time from prescription till death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amitryptiline</td>
<td>After more than 5 months of amitryptiline use, falling problems developed and myoclonus appeared. Extra pyramidal symptoms worsened. Mutism developed after more than 6 months of amitryptiline use.</td>
<td>&gt;8 mths</td>
</tr>
<tr>
<td>2</td>
<td>Haloperidol #, ^ Biperiden # Clozapine ^ Paroxetin^</td>
<td>Became bedridden after 3 weeks of haloperidol, and developed frequent fasciculations affecting all extremities.</td>
<td>4 weeks (haloperidol)</td>
</tr>
<tr>
<td>3</td>
<td>Pipamperon Amantadine # Selegilline #</td>
<td>After starting amantadine and selegilline, cognitive and motor decline continued.</td>
<td>4 mths</td>
</tr>
<tr>
<td>4</td>
<td>Broomperidol # Biperiden # Sertraline # Pipamperon</td>
<td>After 11 weeks of broomperidol en &lt;6 weeks of biperiden use, pt. became confused and drowsy and developed hallucinations, EPS and incontinence. Improved after stopping broomperidol and biperiden.</td>
<td>&gt;11 days (pipamperon)</td>
</tr>
<tr>
<td>5</td>
<td>Paroxetine Haloperidol</td>
<td>Became bedfast within days after starting haloperidol. Coordination disturbances and apraxia developed after two weeks.</td>
<td>4 weeks (haloperidol)</td>
</tr>
<tr>
<td>6</td>
<td>Pergolide</td>
<td>7 years</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pipamperon Haloperidol # Risperid #</td>
<td>After increasing pipamperon dose, there was a rapid cognitive deterioration. One week after starting haloperidol and risperidone, myoclonus developed. Became bedfast / sedated after 6 weeks of risperidone use. Difficulty swallowing developed, thus decreasing the fluid-intake.</td>
<td>16 weeks (pipamperon) 10 weeks (haloperidol / risperidone)</td>
</tr>
<tr>
<td>8</td>
<td>Risperidon Clozapine Olanzapine</td>
<td>Became drowsy after starting clozapine. After 4 weeks of olanzapine, ataxia, dysarthria, orofacial dyskinesia and vertical gaze paralysis developed and visual hallucinations increased. Became unconscious after 8 weeks.</td>
<td>8 weeks (olanzapine)</td>
</tr>
<tr>
<td>9</td>
<td>Olanzapine</td>
<td>Soon after starting olanzapine, mobility decreased. Hallucinations and apraxia developed. Became bedfast after 2,5 mths and developed Wernicke-type aphasia. Myoclonus appeared after 3,5 mths</td>
<td>4 mths</td>
</tr>
<tr>
<td>10</td>
<td>Clozapine Haloperidol</td>
<td>Myoclonus appeared and general condition worsened within days after starting clozapine. MNS developed after starting high dose haloperidol.</td>
<td>19 days</td>
</tr>
<tr>
<td>11</td>
<td>Diazepam</td>
<td>11 mths</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Amantadine Haloperidol Clozapine</td>
<td>Confusion, hallucinations and restlessness developed within 4 weeks after amantadine was started. Myoclonus and difficulty swallowing developed after haloperidol. These symptoms worsened after prescribing clozapine; vertical gaze paralysis and axial rigidity appeared. Became unconscious 1 month after starting clozapine.</td>
<td>1 month (clozapine)</td>
</tr>
</tbody>
</table>

# & ^ indicate simultaneously given medication; medication in italics are not considered neuroleptics but have psychotropic effects
DISCUSSION

DLB and CJD share clinical features like cognitive decline, motor disturbances en psychiatric symptoms. The present case series clearly illustrates that it is sometimes difficult to differentiate these two disease entities (Table 2). CJD is known for its rapidly progressive course and its invariably fatal outcome, whereas the decline in DLB is slower and its course can be influenced by management in several ways. Some patients with DLB may benefit from treatment with dopamine or cholinesterase inhibitors, whereas over 50% of LBD patients exposed to neuroleptics experience a severe ‘sensitivity reaction’.

In the present series of twelve patients, there was an association in time between administering neuroleptics and rapid clinical deterioration in 8 out of 9 patients (0.89, CI 0.52-0.99). In these patients the deterioration was presumably mistaken for signs of CJD instead of an adverse event of drug use. Because of this misinterpretation, the responsible drugs were not stopped or tapered; on the contrary, the dose of the neuroleptic drugs was sometimes increased, leading to further deterioration that was taken to support the clinical suspicion of CJD.

The data presented in this study were retrospectively collected and this seriously limits the interpretation of the causal nature of the relations that we describe. We were dependent on the data available in case records or other forms, and these data were not always detailed enough for making a diagnostic classification. On the other hand, we think that the results of this case series represent a valid and sobering reflection of daily neuropsychiatric practice in the Netherlands. Awareness of a diagnostic algorithm and sensible use and interpretation of ante-mortem diagnostic tests (EEG, 14-3-3 protein in CSF, MRI) should improve the diagnostic procedure. A national CJD surveillance unit which provides clinicians with information on the diagnosis of CJD can be of great importance in this matter. In Europe these services are available nowadays in many countries.

There are several earlier reports on patients with autopsy-confirmed DLB who had been clinically suspected to suffer from CJD. The present series of patients suggests that it may be specifically the neuroleptic sensitivity in DLB that plays a role in this diagnostic pitfall. Diagnostic confusion between CJD and DLB may have important consequences: a false positive clinical diagnosis of ‘probable’ or ‘possible’ CJD may lead to treatment restrictions and because of this DLB patients may never receive appropriate symptomatic treatment.

Neuroleptics are widely used to treat psychiatric disturbances in elderly patients with dementia. Prescription rates of more than 50% have been reported. Neuroleptic sensitivity, operationalised as rigidity, sedation, increased confusion and sometimes pyrexia starting after administration of neuroleptic drugs, is a supportive feature of DLB and associated with increased morbidity and mortality.
In case of an unclassified neurodegenerative disease, worsening of cognitive and motor symptoms after administering neuroleptic drugs should lead to consider the diagnosis of neuroleptic sensitivity reaction in the context of DLB, rather than CJD.

References


