Vascular factors in dementia: prevention and pathology
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Dyshoric capillary cerebral amyloid angiopathy mimicking Creutzfeldt - Jakob disease
Abstract

**Background:** Subjects fulfilling the World Health Organisation diagnostic criteria for Creutzfeldt-Jakob disease (CJD) often have a different diagnosis at autopsy, including Alzheimer's disease. Cerebral Amyloid Angiopathy (CAA) is a common finding in Alzheimer's disease, and in rare cases this is particularly capillary CAA with dyshoric changes.

**Methods:** Of 225 suspected CJD cases, six had extensive capillary CAA with dyshoric changes, in addition to neurofibrillary tangles and in the absence of CJD pathology. Clinical data and results of neuroimaging, electroencephalography and cerebrospinal fluid analysis were collected to assess what led to the erroneous clinical diagnosis of CJD.

**Results:** All six patients had a rapidly progressive dementia (mean 8.2 months, range 3-24). Four fulfilled criteria for 'probable' and one for 'possible CJD'. 14-3-3 Protein in CSF and/or EEG-findings supported the suspicion of CJD in five patients.

**Discussion:** Patients with a clinical suspicion of CJD, supported by EEG and/or CSF abnormalities can have severe capillary CAA with dyshoric changes in addition to the presence of neurofibrillary tangles. Possibly dyshoric capillary CAA can contribute to rapid clinical progression in dementia.
Background

The clinical diagnosis of ‘possible Creutzfeldt-Jakob disease’ (CJD) is based on a combination of symptoms and signs, with rapidly progressive dementia as the core feature, accompanied by at least two of the following symptoms: myoclonus, visual or cerebellar signs, pyramidal or extra-pyramidal signs and akinetic mutism. For the diagnosis ‘probable CJD’ additional findings of periodic sharp wave complexes (PSWCs) in the electro-encephalogram (EEG) or the detection of 14-3-3 protein in the cerebrospinal fluid (CSF) is required.\(^1\) Abnormalities on magnetic resonance imaging (MRI) can support the clinical suspicion of CJD, but are not required to fulfil the WHO criteria.\(^2\) Of all clinically suspected CJD cases, only about 30% have CJD at autopsy.\(^3\) In the CJD-registry of The Netherlands, a small group was noticed with a remarkably extensive capillary cerebral amyloid angiopathy (CAA).

CAA is a common neuropathological finding in non-demented elderly subjects, and occurs in as much as 70-100% of the AD cases.\(^4\) Depositions of Amyloid-β (Aβ) occur mostly in leptomeningeal arteries and arterioles, but in some subjects predominantly the cortical capillaries are affected (capCAA), with Aβ deposits spreading into the surrounding neuropil in flame-like depositions, so-called dyshoric angiopathy.\(^4\) CapCAA occurs in all CAA stages, in both demented and non-demented subjects, but its prevalence has not systematically been investigated.\(^5\) Whether dyshoric capCAA can lead to neurological symptoms and signs is currently unknown.

This case-series describes six patients who were clinically suspected of having CJD, but in whom extensive capillary cerebral amyloid angiopathy (capCAA) with dyshoric changes, neurofibrillary tangles and relatively little parenchymal Aβ plaques were found at post-mortem examination. Clinical characteristics and results of ancillary investigations are reported in order to gain insight into the clinical profile of these patients that had led to the –erroneous– clinical diagnosis of CJD.

Methods

Subjects

All patients with a suspicion of CJD in the Netherlands in whom consent for autopsy is obtained are referred to the University Medical Centre (UMC) in Utrecht for pathological examination. From 2001 to 2008, brains of 225 patients were examined. In 115 patients (51 %) the diagnosis of CJD was confirmed. In 6 of the 110 cases (5.4%) with other diagnoses severe dyshoric capCAA with extensive spread of Aβ into the neuropil was found, in addition to relatively few or no plaques and in the absence of CJD pathology.
Neuropathological evaluation

All neuropathological stainings were performed in a standardized way. Haematoxylin-eosin and luxol-PAS stainings were performed on seven cortical areas, basal ganglia, thalamus, mesencephalon, pons, medulla, vermis and cerebellum/dentatus. For PrP detections frontal, occipital and parietal cortex, basal ganglia and vermis were immunohistochemically stained with 3F4 antibodies (1: 400, mouse mab, Signet) after prot.K pre-treatment. Abeta (A\(\beta\) 1-17 1: 400 mouse mab, DAKO) and tau (AT8, 1: 250 mouse mab, Innogenetics) stainings were performed and severity of tau pathology was scored according to Braak and Braak.\(^6\) Staining with Congo-red and immunohistochemical staining with anti-A\(\beta\) 1-17 were used to assess severity of A\(\beta\) deposits in plaques, CAA and dyshoric changes.

Clinical data

Clinical data were collected retrospectively, using all medical files that could be retrieved from physicians who referred patients for autopsy. Informed consent for use of the data and tissue for research was obtained from relatives of all patients. Demographical data and relevant clinical characteristics were extracted. Results of CSF analysis including 14-3-3 protein, MRI and computed tomography (CT) of the brain and EEG were reviewed.

Results

Clinical characteristics

All six patients suffered from a rapidly progressive dementia, the main reason for considering a diagnosis of CJD. The mean disease duration was 8.2 months (range 3 – 24 months) and the mean age at onset was 77.2 years (\(SD=5.5\); range 70-86, Table).

<table>
<thead>
<tr>
<th>Nr</th>
<th>Sex</th>
<th>Age</th>
<th>Duration (months)</th>
<th>MC</th>
<th>Visual/cerebellar</th>
<th>PS/EPS</th>
<th>AM</th>
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<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>80</td>
<td>24</td>
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</table>

Patient characteristics, results of ancillary investigations and fulfilment of World Health Organization CJD criteria.[1] MC: myoclonus; PS: pyramidal signs; EPS: extra-pyramidal signs; AM: akinetic mutism; PSWC: periodic sharp wave complexes on EEG; CJD: Creutzfeldt-Jakob disease; PC: pleiocytosis; n.p: not performed. ICH: intracerebral haemorrhage.
Five patients had akinetic mutism and five patients had myoclonus. Three patients had pyramidal or extra-pyramidal signs. Seizures and aphasia were reported in several of the patients (Table).

**Ancillary investigations**

EEG was obtained in five of the six patients (Table): four EEG’s showed periodic sharp wave complexes (PSWC). One patient had only non-specific EEG changes described as general slowing, not supportive for the diagnosis ‘probable CJD’.

Five patients had both a MRI- and CT scan; one patient only had a CT scan. None of the MRI scans revealed abnormalities supportive for the diagnosis CJD. Other findings on imaging varied from no abnormalities (one patient) to leukoaraiosis, diffuse cortical atrophy and hippocampal atrophy. The scan of patient 2 revealed three recent infarctions (thalamus, occipital lobe and parietal lobe of the left hemisphere) and the MRI in patient 3 revealed signs of an old intra-cerebral haemorrhage in the right frontal lobe. Lumbar puncture was performed in all but one patient. In three patients the 14-3-3 protein was present in CSF. A slight CSF pleiocytosis (26/mm³ leucocytes) in addition to the presence of 14-3-3 protein was present in patient 5, and severe pleiocytosis (3200/mm³ leucocytes) with an elevated level of CSF protein (3.0 g/l) was found in patient 6.

**Diagnostic criteria**

In retrospect, following the World Health Organisation (WHO) criteria for the classification of sporadic Creutzfeldt-Jakob disease¹, four of the six patients could be classified as ‘probable’ CJD, one patient as ‘possible’ CJD (no CSF or EEG was performed) and one patient did not fulfil the criteria. (Table)

<table>
<thead>
<tr>
<th>Other PSWC</th>
<th>14-3-3</th>
<th>Criteria CJD</th>
<th>CT/MRI</th>
<th>Other CSF findings</th>
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<tr>
<td>-</td>
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<tr>
<td>seizures</td>
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<td>probable</td>
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<tr>
<td>aphasia, apraxia</td>
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<td>probable</td>
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<tr>
<td>apraxia, consciousness ↓</td>
<td>-</td>
<td>probable</td>
<td></td>
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<tr>
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<td>-</td>
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</tr>
<tr>
<td>n.p.</td>
<td>-</td>
<td>-</td>
<td>old ICH right frontal lobe</td>
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</tr>
<tr>
<td>generalized atrophy</td>
<td>n.p.</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>slight PC</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>possible</td>
<td>-</td>
<td>-</td>
<td>no abnormalities</td>
<td>severe PC, ↑ protein</td>
</tr>
</tbody>
</table>
Neuropathology

All subjects had extensive neurofibrillary tangles consistent with Braak stage three to six. Although Braak stage four to six is compatible with the neuropathological criteria for AD, few or no plaques were seen, which is very uncommon for classic AD patients with advanced dementia. The extensive capCAA, with severe dyshoric changes was the most remarkable finding in this series. (Figure)

Discussion

In 51% of patients the clinical suspicion of CJD could be pathologically confirmed, which is higher than in previous series. Our finding of severe capCAA as most prominent neuropathological characteristic in a small proportion of patients with another diagnosis has not been reported before. Rapidly progressive dementia led to the clinical suspicion of CJD in all six cases. Additional symptoms including akinetic mutism, visual hallucinations and myoclonus
were compatible with this diagnosis in all six patients. In most cases, EEG and/or CSF findings were also supportive for the diagnosis CJD. According to the WHO-criteria for CJD, it was justified that this diagnosis was considered in five out of the six patients (four probable and one possible CJD). One patient did not fulfil diagnostic criteria, but in this patient the combination of rapidly progressive dementia with akinetic mutism, focal cortical disturbances (aphasia) and PSWCs on EEG understandably led to the clinical suspicion of CJD. Especially the interpretation of the EEG and CSF abnormalities have probably contributed to the erroneous diagnosis. PSWCs are not specific for CJD and occurrence of ‘CJD-like EEG’s’ can occur in several other neurological diseases, including AD. The presence of 14-3-3 protein in CSF can support the clinical suspicion of CJD with high sensitivity and specificity, but this only holds true in patients, in whom encephalitis, recent stroke and central nervous system (CNS) malignancies have been excluded.

Patient 2 had three recent infarctions that can explain the rapid clinical deterioration and patient 6 had a severe pleiocytosis, compatible with a CNS infection. Although CSF pleiocytosis is not present in CJD, it is understandable that the mild pleiocytosis in patient 5 did not lead to disregarding this diagnosis. In retrospect three of the six cases fulfilled the WHO clinical criteria for probable CJD, one case did not, but did have symptoms compatible with the diagnosis and supportive EEG abnormalities, and in two patients the diagnosis should have been disregarded based on other findings of ancillary investigations (recent infarctions and severe pleiocytosis).

Although sporadic CAA is, apart from lobar haemorrhages, mostly considered to be a-symptomatic, several cases of severe CAA with rapidly progressive dementia and seizures, as well as a steroid-responsive inflammatory encephalopathy, have been reported. In four out of six of the described patients no other plausible explanation for the rapidly progressive dementia was found, suggesting that possibly the capCAA with spreading of the Aβ deposits into the neuropil, could have contributed to the rapid clinical deterioration. CNS infection and recent multiple cerebral infarction could have contributed to the rapid clinical deterioration in the two other patients. Although the six cases exhibited extensive neurofibrillary tangles, they had very little parenchymal Aβ-plaques, distinguishing them from regular AD cases. In addition, the rapid progression of dementia is highly atypical for AD. Few cases of extremely rapid progression in AD with neuropathological confirmation have been reported before and at least one of these had CAA, but capillary involvement and dyshoric changes were not mentioned.

The small number of cases in this series obviously precludes a definitive conclusion on the nature of the relation between dyshoric capCAA and rapidly progressive dementia. CapCAA has been described in AD patients, without reporting many details about the clinical features of the patients and the same holds for subjects with extensive dyshoric capCAA. Larger autopsy series of demented patients and controls should be systematically investigated for the presence of capCAA, in order to characterise in more detail the association between rapidly progressive dementia and presence of capCAA.
References


