LETTER

Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease

INTRODUCTION

Psychotic symptoms may occur in any dementia, including Alzheimer's disease (AD), but are particularly common in Lewy body dementia (LBD). The mechanisms of psychotic symptoms are largely unknown. Psychosis has been found to be associated with more severe AD and Lewy body pathology in patients with AD and cerebrovascular disease-related vasculopathy.[1] One form of vascular pathology, cerebral amylod angiopathy (CAA), is defined as deposits of amyloid in the vessel walls that increase risk of haemorrhage and ischaemia. CAA contributes to neurodegeneration, but its relation to clinical symptoms and course in dementia is not fully understood.[2]

The aim of this study was to investigate the postmortem pathological correlates of severe psychotic symptoms in moderate AD and LBD, which were followed annually from the time of diagnosis until death.

METHODS

This is a 12-year prospective follow-up study of dementia ending in neuropathological examination. The 223 patients of the dementia study in Western Norway (Demvest) were diagnosed as mild dementia and followed annually with standardised clinical assessments until death. Patient were diagnosed according to standardised clinical criteria for AD[3] and DLB[4] or PDD (both combined as LBD) and mild dementia defined as Mini Mental Status Examination (MMSE) score of at least 20 or a Clinical Dementia Rating scale global score=1. The procedures are described in detail elsewhere.[5] All comparisons are between groups are based on pathological defined diagnosis.

The validated Norwegian 12-item Neuropsychiatric Inventory (NPI) was used to assess neuropsychiatric symptoms. Presence of severe psychosis was based on the first 5 years after diagnosis and MMSE value above 10. NPI score of >4 on either item 1 (delusions) or 2 (hallucinations) was used as clinical significant cut-off.

Brain dissection, macroscopic description, regional sampling, tissue processing and staining were done following standard protocols including BrainNet Europe and Brains for Dementia Research UK. Cerebral amyloid angiopathy (none to mild as no, moderate to severe as yes) and small vessel disease (none to mild as no, moderate to severe as yes) were scored according to Vascular Cognitive Impairment Neuropathology Guidelines and BrainNet Europe guidelines.[6 7] The autopsy cohort did not differ significantly from the non-autopsy cohort for gender, education and baseline MMSE score but was slightly younger and had longer survival.[8] Associations were tested using Fisher's exact (binomial) and Mann-Whitney U tests (MW; continuous).

RESULTS

Of the first 50 cases autopsied, 31 were pathological diagnosed as AD and 16 as LBD. Four patients (two AD and two LBD) used antipsychotic drugs. Baseline measurements and survival time are shown in table 1. Of note, AD patients

Table 1 Baseline variables, survival time and pathology scores of early and severe psychosis in Alzheimer's disease and Lewy body dementia

		Alzheimer's disease		Lewy body dementia	
		Severe psychosis	No psychosis	Severe psychosis	No psychosis
		(n=14)	(n=17)	(n=10)	(n=6)
Gender, male/female, n		5/9	5/12	6/4	5/1
Age at baseline, years mean (SD)		75(8)	72(9)	74(9)	74(6)
Duration of disease, years mean (SD)		2.2 (2.5)	2.3 (1.7)	3.1 (2.1)	1.3 (1.0)
MMSE, score mean (SD)		23.9 (2.4)	25.3 (1.8)	24.1 (3.2)	24.7 (3.7)
NPI, total score mean (SD)		25 (23)	29 (27)	37 (22)	23 (17)
Survival time, mean (SD)		**6.9 (1.4)***	**8.4** (1.5)	4.7 (2.15)	4.3 (1.9)
Annual decline MMSE, mean (SD)		3.33 (1.44)	2.86 (1.21)	3.46 (2.02)	1.39 (3.31)
Hallucinations present, n		11	–	9	–
Delusions present, n		10	–	8	–
Neuropathology, n					
CERAD	0–B	0	2	6	4
	C	14	15	4	2
Braak tau stage	0–4	0	4	6	4
	5–6	14	13	4	2
Braak alpha-synuclein	0–4	11	12	1	0
	5/6	3	5	9	6
Cerebral amyloid angiopathy	No	**3**	**10**	5	5
	Yes	**11***	**7**	5	1
Small vessel disease	No	**3**	**11**	5	2
	Yes	**11***	**6**	5	4

Baseline, survival and pathological scores of patients followed annually for up to 12 years with both Alzheimer's disease and Levy body dementia defined by pathological diagnose.
*P<0,05 on Fisher's exact (binomial) or Mann-Whitney U test.
†Patients with early and severe psychotic symptom identified as >4 score on NPI items 1 or 2 with MMSE >10.
‡Cerebral amyloid angiopathy and c small vessel disease was scored no (none and mild) or yes (moderate and severe) according to Vascular Cognitive Impairment Neuropathology Guidelines.
CERAD, Consortium to Establish a Registry for Alzheimer Disease neuritic plaques class; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory.

with psychosis had shorter survival than those without.

There were no significant associations between psychosis and amyloid plaques, tau or alpha-synuclein pathologies in the total group or in AD and LBD groups separately. Advanced SVD (p=0039) and CAA (p=0029) were more prominent in AD patients with psychosis, compared with AP patients without psychosis. There were no significant associations between vascular and neurodegenerative pathologies. There were no significant associations between either vascular or other pathologies and psychotic symptoms in patients with LBD.

CAA alone, but not SVD, showed significant associations with mean NPI item score of delusion (p=0028, MW) and hallucination (p=0031, MW) in AD. Patients with both CAA and SVD had higher item scores of delusions and hallucinations than those with one or none of the vascular pathologies. There were no significant associations between either vascular pathologies and annual cognitive decline or last observed MMSE in AD. Among the 41 patients with apolipoprotein E (ApoE) genotype available, no significant association to vascular pathology or psychosis was found.

To allow for comparison with other studies, associations between pathological scores and psychotic symptoms present at the last observation or present ever during the study period were explored, but no significant associations were found.

DISCUSSION

The main finding in this study was the association between advanced CAA and SVD with severe psychotic symptoms in moderate AD. To our knowledge, this is the first report on a potential link between CAA and psychotic symptoms in AD.

CAAs are amyloid (usually amyloid-beta) deposits in vessel walls that constrict vascular lumen and may cause life-threatening lobar haemorrhages through weakening of the vessel wall. Some degree of CAA is often present in patients with AD. CAA can also contribute to neurodegeneration and cognitive dysfunction through microbleeds.[2] Our sample had considerable comorbid vascular pathology, but all patients with AD fulfilled both clinical and pathological criteria of AD. There was no significant associations of vascular pathologies and severity of AD pathology.

Subcortical arteriosclerotic leukoencephalopathy (SVD-related pathology) and vascular risk factors, but not specific vascular pathologies, were found associated with psychosis ever present.[1] Vascular changes on MRI have also been associated with late onset schizophrenia, and there is an overlap between late onset schizophrenia and early psychotic symptoms in dementia. Microvascular abnormalities are also found in schizophrenia, further supporting the vascular dysfunction element of psychosis.

Interestingly, the neuropsychological profile of both CAA and SVD in patients without clinical dementia is characterised by decreased processing speed, which is also found in psychotic diseases, and previous episode of psychosis is by far the strongest risk factor for development of psychosis in AD. Thus, vascular pathology and reduced information processing speed may be a risk factor of psychosis in dementia that are modifiable by cardiovascular disease prevention.

Clinically misdiagnosed patients with dementia may be an important subgroup inflicting errors in trials and mixed AD with vascular dementia are often misdiagnosed as pure LDB.[1] Our findings of vascular pathology and severe psychosis introduce a possible understanding of this subgroup and may improve diagnostic accuracy.

Causative conclusions about pathological associations with early symptoms cannot be drawn from postmortem studies alone due to end-stage pathological data. Cerebrovascular pathologies take many years to develop and are associated with lifestyle and genetics risk factors. We found no association between vascular pathology and ApoE genotype. Epidemiological and clinical studies show evidence for increased peripheral inflammatory markers in psychosis spectrum disorders,[9] and systemic inflammation is known to contribute to cerebrovascular pathologies and cognitive impairment. Therefore, inflammation may be a possible link between vascular pathology and psychosis in dementia. Long-term antipsychotic use, which may accelerate cerebrovascular disease, was low in our sample due restrictive national guidelines.

Strengths of the study include the prospective design with inclusion of patients from time of diagnosis, allowing us to identify those with early psychosis, and the selection of an unbiased cohort for autopsy, which did not differ from those without autopsy.[8] Limitations of the study are the relatively small sample size with a risk of type II error, and there are no region-specific assessments of vascular pathologies.

In conclusion, severe psychosis in moderate AD is associated with advanced SVD and CAA postmortem. Accordingly, identifying and treating vascular disease and risk factors could reduce the emergence of psychosis in patients with AD.

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Contributors Study concept and design: all authors. Gathering of data: AOV-M, TH, JB and DA. Analysis and interpretation of data: AOV-M, TH, CB and DA. Drafting of the manuscript: AOV-M and DA. Critical revision of the manuscript: all authors.

Funding This study was funded by Norwegian Health Association.

Competing interests AOV-M, JB and TH declare that they have no conflict of interest. CB has received grants and personal fees from Acadia and Lundbeck, personal fees Heptares, Roche, Lilly, Otsuka, Orion, GSK and Pfizer. DA has received research support and/or honoraria from Astra-Zeneca, H Lundbeck, Novartis Pharmaceuticals and GE Health and serves as paid consultant for H Lundbeck, Eisai and Axovant.

Patient consent Obtained.

Ethics approval The regional committee for medical and health research ethics in western Norway approved of the study (REK 2010/633). All patients signed informed consent to participate in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Vik-Mo AO, Bencze J, Ballard C, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2018-318445

Received 18 March 2018
Revised 28 June 2018
Accepted 10 July 2018

J Neurol Neurosurg Psychiatry 2018;**0**. doi:10.1136/jnnp-2018-318445

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