Table 1 Number of ward admissions, patient demographics and duration of ward stay per ward admission in each diagnostic group

Diagnostic group	Admissions, n	Patients, n	Age (years)	Women, n	Ward stay (days)
Non-organic	48† (7)	45 (8)	39 (14–74)*	37 (77)*	5 (1–7)
Organic	633† (92)	506 (90)	54 (17–89)	279 (44)	5 (1–147)
Uncertain	9 (1)	9 (2)	30 (17–59)	9 (100)	3 (2–8)
Unknown	3 (<1)	3 (<1)	28 (17–50)	2 (67)	4 (2–4)

Values are n (%) or median (range).

* $p < 0.001$ between non-organic and organic diagnostic groups.

†Multiple admissions; 3/45 and 90/506 patients with non-organic and organic diagnoses, respectively, were admitted two or more times during the study period.

stay, age, sex, referral source, presenting symptoms, investigations used, the information provided to the patient by the neurology team about their diagnosis and whether the patient was subsequently referred for a psychiatry opinion.

For a small number of cases, this latter information was not available (because the relevant outpatient correspondence could not be obtained from another hospital). This is reflected in our analysis by the variable denominator given in the Results section for these outcome measures.

The Mann-Whitney U test was used to determine whether significant differences ($p < 0.05$) existed between non-organic and organic admissions for age and duration of ward stay.

Results

A case note review of all admissions from list 2 and of a random sample (80/380) from list 1 identified 45 of 313 and 3 of 80 admissions with a non-organic diagnosis, respectively. The total number of non-organic ward admissions therefore identified in our sample was 48 of 693 (7%, $n = 45$, table 1). None of these 48 admissions was given a non-organic DCT by the hospital coding office. As the DCT error rate on the partially sampled list 1 is 4%, we predict that the true percentage of non-organic admissions in our total sample of 693 admissions is 9%.

In all, 23 of 48 (48%) of the non-organic admissions were emergencies: 7 of 48 from GPs; 15 of 48 transferred from a district general hospital (14/15 patients first presenting to the Accident and Emergency department); 1 of 48 (non-epileptic seizure) from the hospital radiology department. Admissions that were transferred to the neurology ward from a district general hospital had a median duration of hospital stay at their referring hospital of 6 days (range 1–21, $n = 13$).

No marked difference was observed in the duration of ward stay either between non-organic and organic admissions (table 1) or between non-organic admissions admitted electively (median 5, range 2–12 days) and non-organic admissions admitted as an emergency (median 5, range 1–17 days).

In all, 30 of 48 (63%) non-organic admissions were for possible epileptic seizures (elective admissions, $n = 17/25$ (68%); emergency admissions, $n = 13/23$ (57%)). Sensorimotor disturbance in the limbs (including gait disturbance) and movement disorders together accounted for nearly one-third of non-organic admissions (29%).

The investigations most often carried out were a standard electroencephalogram recording in 31 of 48 (65%) cases and a period of videotelemetry in 24 of 48 (50%)

cases. All 17 elective, and 6 (46%) of emergency non-organic admissions with a possible history of seizures, underwent a period of videotelemetry during their admission. Videotelemetry seemed to be a useful investigation, capturing a sample of a patient's non-epileptic attacks in over 80% of cases. Other commonly used investigations included MRI (25%), lumbar puncture (17%) and neurophysiological studies (15%).

Twenty six of 43 (60%) non-organic admissions were subsequently referred for psychiatric support. The fact that the patient had been told directly by medical staff that his or her symptoms were psychological in origin was recorded only in communications to the GP in just over half—that is, in 25 of 43 (58%) of the admissions. Most of these (18/25 (72%)) patients were subsequently referred to psychiatric services.

Discussion

Consistent with a recent report,⁴ this study has shown that 9% of inpatients on a tertiary referral neurology ward are likely to have a non-organic disorder. Half of these are admitted as an emergency, often first presenting to an Accident and Emergency department.

These patients are as “costly” as patients with organic disease in terms of the duration of ward stay, and place a major burden on resources. Importantly, as the DCTs assigned by the hospital coding office did not identify any of the non-organic admissions, the future resource needs for these patients may be underestimated.

A history of possible seizures accounted for most non-organic admissions. Although videotelemetry was helpful in the investigation, because of resource limitations this was possible only in approximately half of the relevant emergency admissions.

Despite the potential benefits of referral to psychiatric services, 40% of non-organic admissions were not referred after their diagnosis. Our findings highlight the need for designated psychiatric services for these inpatients.⁵ A more transparent disclosure of the diagnosis directly to the patient by the neurology team may also facilitate the ongoing care of the patient by the GP in the community.

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Selective reduction of amyloid β 42 discriminates Alzheimer's disease from Huntington's disease: indication for distinct pathological events in amyloid β peptide aggregation

Huntington's disease and Alzheimer's disease are neurodegenerative disorders associated with the aggregation of misfolded polypeptides, leading to amyloids and neuronal damage.¹

Huntington's disease is caused by expanded glutamine repeats that encode polyglutamine tracts of the gene encoding the huntingtin protein, and is associated with dementia. Polyglutamine tracts in Huntington's disease form amyloid structures in the cerebral cortex and in the striatum.²

In Alzheimer's disease, extracellular amyloid β (A β) peptides form amyloid plaques in the brain, and lower levels of A β 1–42 in the cerebrospinal fluid (CSF) may reflect neuro-pathological processes in amyloid-related

Figure 1 Amyloid β protein ($\text{A}\beta$) sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) immunoblot with urea (A) and conventional SDS-PAGE without urea (B) of CSF (lane 1–5) and mix of synthetic $\text{A}\beta$ peptides 1–37, 1–38, 1–39, 1–40, and 1–42 (lane 5). Ten microliters of unconcentrated CSF of patients one each with HD (lane 1), OC (lane 2), NNC (lane 3) and AD (lane 4), respectively were applied. *The migration position of as yet unidentified $\text{A}\beta$ peptides.

disorders. A quantitative urea-based $\text{A}\beta$ -sodium dodecylsulphate-polyacrylamide gel electrophoresis with western immunoblot ($\text{A}\beta$ -SDS-PAGE/immunoblot) recently showed the regular abundance of Ct-truncated $\text{A}\beta$ peptides in the CSF and displayed disease-specific variations.^{3,4}

The morphological substrate of dementia in Huntington's disease is controversial, and concomitant Alzheimer's disease pathology has been discussed.⁵ Thus, Alzheimer's disease and Huntington's disease share pathological similarities and may even culminate in a common mechanism of pathogenesis or concomitance in which these protein aggregates affect cellular functions and cause neuronal death.

Methods

Of the 69 patients in the study, 16 had Huntington's disease, 16 had Alzheimer's disease, 20 had other choreatic diseases and 17 were neurological controls without dementia. Mean age did not differ significantly between diagnostic groups, except between those with Alzheimer's disease and those with Huntington's disease ($p = 0.002$). The Mini-Mental Status Examination (MMSE) score was significantly different between the group with other choreatic diseases and that with Alzheimer's disease ($p = 0.002$).

Figure 2 Amyloid β ($\text{A}\beta$) concentrations in patients and controls. AD, Alzheimer's disease; HD, Huntington's disease; NNC, neurological controls without dementia; OC, other choreatic diseases.

Clinical diagnosis in patients with Huntington's disease (6 men and 10 women) was confirmed by DNA analysis. Their median age was 56 (range 41–67) years, median disease duration was 36 (range 12–96) months and the median MMSE score of seven patients with dementia was 24 (range 12–29).

We also included 6 male and 14 female patients with normal CAG repetition length and the following diagnoses: idiopathic senile chorea ($n = 2$), tardive dyskinesia ($n = 2$), vascular encephalopathy ($n = 2$), multiple system atrophy ($n = 1$), Wilson's disease ($n = 1$), amyotrophic lateral sclerosis ($n = 1$), paraneoplastic encephalopathy ($n = 1$), bipolar disorder ($n = 1$), frontotemporal dementia ($n = 1$), antiphospholipid syndrome ($n = 1$) and cerebral mucosa-associated lymphoid tissue lymphoma ($n = 1$). In six patients the diagnosis remained unclear. The median age of these 20 patients with other choreatic diseases was 64 (range 19–87) years and disease duration was 24 (range 1–108) months. The median MMSE score of 12 patients with dementia was 27 (range 21–30).

All 16 patients with Alzheimer's disease fulfilled the National Institute of

Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria. Their median age was 63 (range 52–86) years and disease duration 24 (range 6–72) months. The median MMSE score (available for 13 patients) was 17 (range 11–25).

The group of neurological controls without dementia comprised 7 men and 10 women (median age 57, range 18–94 years) who had peripheral neurological diseases ($n = 7$), cerebral transient ischaemic attacks ($n = 2$), spinal cord or radicular diseases ($n = 2$), migraine ($n = 1$), focal epilepsy ($n = 1$), multiple sclerosis ($n = 1$), Lyme borreliosis ($n = 1$), dizziness ($n = 1$) and Hashimoto's thyroiditis ($n = 1$). The median MMSE score was 30.

CSF samples were processed and analysed as published previously.^{3,4} For statistical analysis, we used the Mann-Whitney U test for comparing two cohorts or the Kruskal-Wallis test for comparing more than two groups.

Results

A highly conserved pattern of $\text{A}\beta$ peptides was regularly expressed in the CSF of

Table 1 Absolute abundance and total concentration of $\text{A}\beta$ peptide patterns in the CSF of the diagnostic groups

Diagnostic group	Median (range) concentration [ng/ml]					Total $\text{A}\beta$
	$\text{A}\beta$ 1–37	$\text{A}\beta$ 1–38	$\text{A}\beta$ 1–39	$\text{A}\beta$ 1–40	$\text{A}\beta$ 1–42	
Neurological controls without dementia	0.98 (0.51–1.66)	1.96 (1.21–2.80)	0.93 (0.50–1.78)	9.03 (5.86–11.97)	1.47 (0.56–2.30)	13.05 (8.83–19.47)
Other choreatic diseases	0.71 (0.29–2.61)	1.49 (0.56–3.61)	0.86 (0.27–2.29)	7.55 (2.70–15.03)	0.96 (0.32–2.35)	12.20 (4.32–25.29)
Huntington's disease	0.59 (0.28–2.40)	1.38 (0.66–3.95)	0.66 (0.33–2.72)	5.87 (3.36–16.01)	0.83 (0.27–3.58)	9.39 (5.02–28.01)
Alzheimer's disease	0.77 (0.26–1.40)	1.32 (0.50–3.02)	0.75 (0.25–1.74)	6.16 (2.24–13.38)	0.43 (0.09–0.77)	9.96 (3.40–20.02)

$\text{A}\beta$, amyloid β ; CSF, cerebrospinal fluid.

patients with Huntington's disease and other choreatic diseases. The respective bands appeared only when samples were separated in the presence of urea (fig 1).

The group with Alzheimer's disease had lower levels of A β 1–42 ($p < 0.001$) and A β total ($p < 0.023$) than the group of neurological controls without dementia, and lower levels of absolute A β 1–42 than the heterogeneous group with other choreatic diseases ($p < 0.001$; table 1).

A β 1–42 ($p = 7.1 \times 10^{-5}$) and the ratio of A β 1–42 to A β total ($p = 1.2 \times 10^{-6}$), but not other measured A β peptide, differed significantly between the group with Alzheimer's disease and the group with Huntington's disease, but we found no significant differences in A β between the group of neurological controls without dementia and the group with other choreatic diseases or the group of neurological controls without dementia and the group with Huntington's disease.

A subgroup analysis of patients with Huntington's disease with ($n = 7$) and without ($n = 9$) dementia showed no differences in the CSF A β peptide pattern, but the groups with Huntington's disease and Alzheimer's disease differed significantly in A β 1–42 ($p = 0.005$).

On comparing age and MMSE score with the A β pattern in the groups with Alzheimer's disease and Huntington's disease, we found no significant correlations with any of the measured A β peptides; CAG repeat length in the group with Huntington's disease and in the group with other choreatic diseases did not correlate with any of the measured A β peptide parameters.

Discussion

We analysed the A β pattern with a quantitative A β -SDS-PAGE/immunoblot to investigate CSF samples from 69 patients with Alzheimer's disease, Huntington's disease or other choreatic diseases and neurological controls without dementia with the aim of identifying a distinct A β peptide pattern (figs 1, 2). Decreased levels of A β 1–42 in the CSF have been reported in people with Alzheimer's disease and other aggregopathies.^{3,4} As neither plaques nor neurofibrillar tangles are regularly present in people with prion and Parkinson's diseases, an overlapping condition of Alzheimer's disease is unlikely to be solely responsible for this phenomenon.³

The overlap of disease-specific protein aggregation may be reflected by disease-specific A β peptide patterns in the CSF, which prompted us to investigate this issue.

The decrease in A β 1–42 in the CSF of patients with Alzheimer's disease was initially shown by enzyme-linked immunosorbent assay, which was reconfirmed by A β -SDS-PAGE/immunoblot. A β 1–42 levels were not lower in the group with Huntington's disease or in the group with other choreatic diseases than in the group of neurological controls without dementia. Nevertheless, slightly decreased A β 1–42 levels were found in patients with only Huntington's disease and mild to severe dementia.

Cognitive decline is frequently reported in Huntington's disease, even at an early stage, and published results are at conflict regarding the occurrence of plaque pathology.⁵ The inconsistency of plaque pathology in patients with Huntington's disease, however, may be due to concomitant Alzheimer's disease in some patients and may also explain the reduction of A β 1–42 in patients with only Huntington's disease, whereas the mean value of A β 1–42 in the group with Huntington's disease did not differ significantly from that of the controls. According to our data, Alzheimer's disease pathology is not an early event in patients with Huntington's disease, and the A β peptide metabolism is apparently not completely involved in the occurrence of dementia in patients with Huntington's disease.

Nevertheless, the power of our data is limited by the cross-sectional study design and the lack of neuropathological data. Larger patient groups with neuropathological data are needed to further elucidate the relationship between A β pathology in Huntington's disease and its effect on A β peptides in the CSF.

A β peptide patterns in the CSF, however, vary with specific neurodegenerative diseases related to protein aggregation. Variations are apparently linked to disease-specific pathophysiological pathways related to amyloid precursor protein metabolism.

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