Temporal lobe asymmetry in patients with Alzheimer's disease with delusions

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Abstract

Objective—To test the hypothesis that delusions are associated with asymmetric involvement of the temporal lobe regions in Alzheimer's disease.

Methods—Temporal lobe atrophy was assessed with a linear measure of width of the temporal horn (WTH) taken from CT films. Temporal asymmetry was computed as the right/left (R/L) ratio of the WTH in 22 non-delusional and 19 delusional patients with Alzheimer's disease. Delusional patients had paranoid delusions (of theft, jealousy, persecution). None of the patients had misidentifications or other delusions of non-paranoid content.

Results—The R/L ratio indicated symmetric temporal horn size in the non-delusional (mean 1.05 (SD 0.20), and right greater than left temporal horn in the delusional patients (mean 1.30, (SD 0.46); t=2.27, df=39, p=0.03). When patients were stratified into three groups according to the R/L ratio, 47% of the delusional (9/19) and 14% of the non-delusional patients (3/21; χ^2=5.6, df=1, p=0.02) showed right markedly greater than left WTH.

Conclusions—Predominantly right involvement of the medial temporal lobe might be a determinant of paranoid delusions in the mild stages of Alzheimer's disease.

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Behavioural disturbances are common in patients with Alzheimer's disease even in the milder stages of the disease. Among these, psychotic symptoms such as delusions are particularly frequent[1] and disturbing both to patients and their carers and are often the target of drug treatment. However, their biological basis remains unclear.

Alzheimer's disease is known to affect primarily the medial temporal lobe, and its typical clinical manifestation is early and severe amnesia. Only later the disease spreads to lateral temporal, parietal, and frontal regions, with the corresponding neuropsychological deficits. As a rule, the disease strikes the brain in an asymmetric fashion, some patients showing greater impairment of the right and others of the left brain regions and functions.[2][3] It has been shown that detectable asymmetry of involvement appears early and holds to the later stages of the disease,[4] suggesting that asymmetry of involvement is a stable and pervasive feature of the disease. Moreover, some findings seem to suggest that Alzheimer's disease with asymmetric brain involvement might represent an aetiologically distinct subgroup.[5][6] However, apart from the expected correlation between greater language or visuospatial impairment and more severe left or right brain involvement,[4] other demographic and clinical differences between symmetric and asymmetric patients with Alzheimer's disease have not been consistently shown.[7–10]

An alteration of normal cerebral asymmetries affecting mainly the temporal regions is one of the neurobiological hallmarks of schizophrenia.[11] In this disease, delusions are basic clinical features. Data on asymmetry of involvement in relation to delusions in Alzheimer's disease are sparse, and results are conflicting. Although studies converge on localising the symptom in the anterior (temporal and frontal) brain regions, which side is primarily affected remains unclear. Some studies have indicated bilateral[12] or predominantly left,[13] while others seem to point to a predominantly right involvement. In patients with moderate to severe Alzheimer's disease, Förstl *et al*[14] have reported that some types of delusions are associated with greater atrophy in the right anterior brain regions and preservation of the left regions. In a small clinical series of patients with frontotemporal dementia, a non-Alzheimer's disease degenerative disorder, Edwards-Lee *et al* have shown a disproportionate involvement of the right anterior temporal lobe compared with the left in those cases with more severe behavioural disturbances. Half of these patients had delusions.[15]

The aim of our study was to assess whether delusions are associated with asymmetric involvement of the temporal lobe regions in Alzheimer's disease.

Methods

The subjects were 41 right handed patients with mild (mini mental state examination (MMSE)[16] of 18 or higher) probable Alzheimer's disease[17] consecutively admitted to the Alzheimer's Unit of the IRCCS San Giovanni di Dio, who were enrolled in a prospective study on the natural history of the dementias. After complete description of the study to the subjects, written informed consent was obtained. The diagnosis was made on the basis of a standardised clinical, neuropsychological, and instrumental evaluation[18] that included history collection, complete blood

count, chemistry profile, thyroid function, B12, folic acid, and CT. In addition to the MMSE, the clinical evaluation included an assessment of basic daily functions (bathing, dressing, grooming, eating, walking, and continence) with the Barthel index.[19]

Delusions were assessed with the pertinent subscale of the neuropsychiatric inventory (NPI)[20 21] and defined as the presence during the previous month of at least one of the following beliefs: of being in danger, theft, spouse betrayal, abandonment, that unwanted guests live in the patient's own home, that the spouse is not who he or she claims to be, that where the patient lives is not his or her home, and picture sign. By assessing frequency (score 0 to 4) and severity (score 0 to 3), a global severity score (frequency×severity, score 0 to 12) can be computed. Of the 41 patients, 19 had or had had delusions of any severity (global severity score ≥1) There were no indications of modification of delusional manifestation by drug prescription. In fact, none of the non-delusional patients were on neuroleptic drugs on observation or had been on neuroleptic drugs in the month previous to observation. Of the delusional patients, four were on neuroleptic drugs on admission, but with no or little benefit.

Brain CT was done with a spiral scanner Prospeed S (General Electrics). Slice orientation was on the temporal lobe plane—that is, about 20° caudal to the orbitomeatal line, as described by Jobst *et al*.[22] Thin slices were taken throughout the whole extension of the temporal lobe (from the floor of the middle cranial fossa to the inferior aspect of the orbit), and thicker slices in the remaining rostral part of the brain up to the vertex and in the posterior fossa. Image matrix was 512×512. Scan indices in the temporal lobe region were as follows: time 2 s, 120 kV, 160 mA, slice thickness 2 mm, no interslice gap. Scan indices rostral to the temporal region were as follows: time 2 s, 120 kV, 130 mA, slice thickness 5 mm, no interslice gap. Eight to 10 images were back reconstructed in the temporal lobe region and 16 to 18 rostral to the temporal region. Contrast enhancement was not used in these cases.

The measure of temporal atrophy (radial width of the temporal horn (rWTH) was originally devised as an easy to perform tool that might help in distinguishing patients with early Alzheimer's disease from normal older people and was centred in the anterior part of the temporal horn, anteriorly to the midbrain in the area of the hippocampal head (fig 1). It is defined as the maximum distance between two parallel lines tangent to the borders of the tip of the temporal horn (fig 1). These lines usually form an angle of 30° to 60° with the midsagittal line. Test-retest and interrater reliability were assessed separately for the right and left rWTH measures on CT films of 20 randomly selected patients with Alzheimer's disease (age 76 (SD 8) years; 75% women; MMSE 21(SD 3)) by two of us (CG and GBF). Intraclass correlation coefficients (ICCs) were computed showing satisfactory test-retest (ICCs of 0.98 and 0.99) and interrater (ICCs of 0.95 and

Figure 1   Example of measurement of the radial width of the temporal horn. The slice is chosen where the temporal horn is most evident. Different slices can be used for the right and left measurements, although a case is shown where the same slice was chosen for both sides. The dotted lines represent the tangents to the tip of the horn at its largest point. Arrows indicate the measured widths of the temporal horns.

0.95) reliability. Moreover, we demonstrated sensitivity and specificity of 93% and 95% in the separation of the 41 patients with Alzheimer's disease of this study from 28 non-demented controls of similar age recruited for the validation study of the method. Temporal asymmetry was computed as right/left (R/L) ratio of the RWTH.

None of the patients had lacunar or major infarcts on CT. Leukoaraiosis was assessed on CT films with a standardised visual rating scale[23] blind to clinical data. Leukoaraiosis was defined as present where at least one of the following was present on either side in at least one of the frontotemporal, parietal, and occipital regions: (1) periventricular hypodensity confined to the frontal or occipital horns, (2) surrounding the lateral ventricles, (3) extending to the cortex.

Results

Nineteen (46%) of the patients had delusions. Sociodemographic and clinical features were similar between non-delusional and delusional patients (table). In particular, patients had mild severity of dementia and were completely independent in basic daily functions. Language abilities were also similar between the groups: token test was 28 (SD 5) *v* 27 (5), Boston naming 16 (3) *v* 15 (4), controlled oral word association by letter 16 (4) *v* 14 (8) and by category 17 (6) *v* 15 (5) in non-delusional and delusional patients respectively (p>0.20). The R/L ratio was indicative of symmetric temporal horn size in the non-delusional, and right greater than left temporal horn in the delusional patients (1.05 (SD 0.20) *v* 1.30 (SD 0.46); *t*=2.27, df=39, p=0.03).

Thirty two per cent of the delusional patients had severe delusions (NPI score 9 to 12), 31% moderate (NPI score 4 to 8), and 38% mild (NPI score 1 to 3). All delusional patients had

Table 1 Sociodemographic and clinical features of 41 patients with Alzheimer's disease

	Non-delusional (n=22)	Delusional (n=19)	p Value
Age (mean (SD))	74 (8)	76 (8)	NS
[range]	[62–86]	[57–85]	
Female sex (n (%))	14 (64%)	17 (90%)	NS
Years of education (mean (SD))	6 (3)	6 (3)	NS
[range]	[2–17]	[3–13]	
Mini mental state examination (mean (SD))	21 (3)	22 (3)	NS
[range]	[18–26]	[18–27]	
Barthel index (mean (SD))	97 (4)	96 (6)	NS
[range]	[85–100]	[80–100]	
Leukoaraiosis (n (%))	7 (32%)	5 (26%)	NS

NS=p>0.05 on χ^2 or t test.

theft delusions, in six out of 19 associated with another type of delusion, always of the paranoid type (persecution or jealousy). None of the patients had misidentifications or other delusions of non-paranoid content.

Figure 2 shows the crude data of the right and left rWTH. Delusional patients had right rWTH on average significantly greater than the left (6.9 (SD 1.8) v 5.7 (SD 1.5); t=2.21, df=18, p=0.04), while non-delusional patients had similar right and left rWTHs (6.0 (SD 1.7)

v 5.8 (SD 1.9), t=0.44, df=21, p=0.66). Figure 2 shows that, when patients were stratified into three groups according to R/L ratio, delusional patients were more likely to have right markedly greater than left (R/L ratio>1.25) temporal horns. Significance was retained when the two groups of R/L ratio<0.75 and 0.75<R/L ratio<1.25 were collapsed together (χ^2=5.6, df=1, p=0.02).

Discussion

The present results indicate that patients with mild Alzheimer's disease with delusions more often have asymmetric (right greater than left) temporal horns, suggesting that patients with Alzheimer's disease with prominent involvement of the right temporal lobe might be more prone to develop delusions.

Many studies have considered the issue of the brain pathological correlates of psychotic symptoms in primary psychoses such as schizophrenia,[24] indicating an association with a reduction of the normal left greater than right asymmetry. By contrast, data are scant for psy-

	χ^2 = 7.2, df = 2, p = 0.03

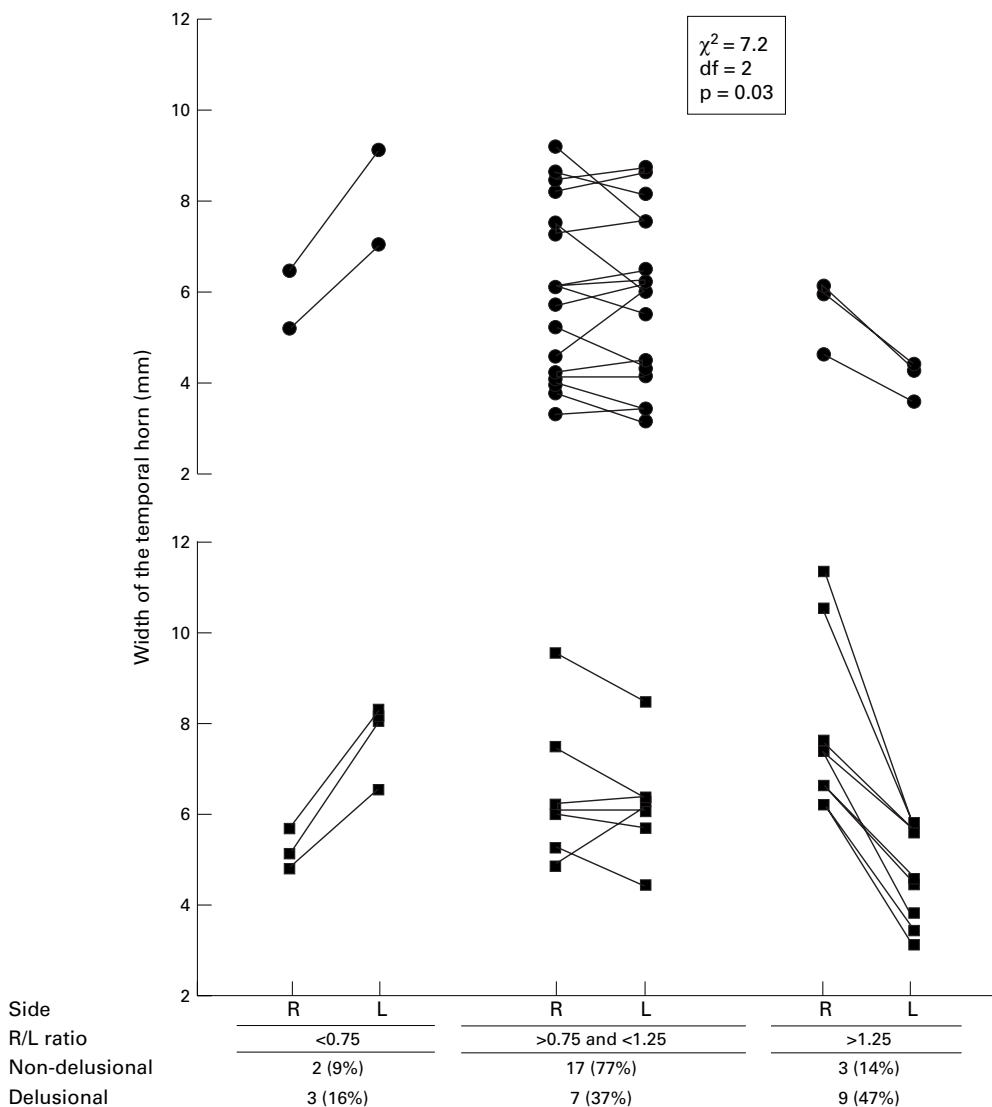| Side	R	L		R	L		R	L
R/L ratio	<0.75			>0.75 and <1.25			>1.25	
Non-delusional	2 (9%)			17 (77%)			3 (14%)	
Delusional	3 (16%)			7 (37%)			9 (47%)	

Figure 2 Radial width of the temporal horn (rWTH) in 22 non-delusional (circles) and 19 delusional (squares) patients with Alzheimer's disease by right/left ratio.

chotic symptoms associated with dementia or other neuropsychological disturbances. The most consistent findings are for Capgras syndrome (the delusional belief that someone is not whom he or she claims to be), which has been associated with vascular lesions of the right temporal lobe.

In Alzheimer's disease, available studies are heterogeneous and poorly comparable for the different psychotic symptoms that were studied and for the different disease severity of the study samples. Forstl *et al*[14] have found that delusional misidentifications in patients with moderate to severe Alzheimer's disease were associated with EEG and CT signs of greater right frontal and temporal damage. With the use of functional imaging techniques, Starkstein *et al*[12] found medial temporal hypoperfusion on SPECT in patients with Alzheimer's disease with delusions, but the finding was bilateral and symmetric. By contrast,, Kotrla *et al*[13] reported an association between psychosis and left frontal and parietal hypoperfusion. However, in these studies disease severity was greater than in our patients with Alzheimer's disease. Moreover, delusions were defined on the basis of the psychiatric diagnostic and statistical manual definition (fixed, false belief not attributable to the patient's cultural experience)[25] which encompasses a large array of behavioural disturbances, ranging from paranoid delusions, to misidentifications, to environmental or person reduplications.[12] By contrast, our patients were in a mild stage of disease severity, and delusions were only of the paranoid type. Indeed, paranoid delusions are known to be more frequent early in the course of the disease,[26] whereas other types of delusions such as misidentifications become frequent only later, in the moderate to severe stages of Alzheimer's disease. The biological basis might also be different, as misidentifications have been shown to be associated with more prominent loss of CA1 hippocampal neurons, and paranoid delusions with less pronounced cortical atrophy.[27]

The present results can be linked to recent data on genetic factors and risk of psychosis in Alzheimer's disease. Harwood *et al*[28] have found that apolipoprotein E (ApoE) ε4 carriers had twice the risk of developing psychosis early in the dementia course than non-carriers. We have recently found that hippocampal atrophy was more marked on the right side of patients with Alzheimer's disease carrying the ε4 allele.[29] Although the association between ApoE genotype and psychosis is controversial,[30] these findings lead to the hypothesis that the higher prevalence of psychosis in our patients with asymmetric right more than left medial temporal atrophy might be due to higher prevalence of ε4 carriers in the delusional group.

Another possible interpretation of our data places delusions in the context of the neuropsychological changes of Alzheimer's disease. Theft delusions, the most prevalent delusional type in our patients, are probably related to insight of the memory disturbance. It is common observation that patients with Alzheimer's disease with poor awareness of their memory problem try to justify their failures by attributing them to others. Insight of disease in Alzheimer's disease is thought to be more impaired in patients showing prominent involvement of the right hemisphere.[31][32] Therefore, right hemispheric involvement might be responsible for poor insight which, in turn, might cause delusional ideas. The connection between delusions and insight might be further substantiated by recent findings in schizophrenia, in which persecutive delusions have been interpreted as disorders of insight.[33][34]

Two caveats should be underlined in the interpretation of these data. Firstly, we cannot exclude that the predominantly right temporal atrophy reflects a more generalised right hemispheric atrophy. Future studies will need to take measures of global atrophy as well as that in regions outside the temporal lobe. Secondly, it should be underlined that about half of our delusional patients failed to show predominantly right temporal atrophy. Environmental factors such as quality of family caregiving,[35] appropriateness of physical environment,[36][37] or premorbid personality features[38] might be involved in the genesis and in the modulation of behavioural disturbances. Further studies will need to assess the contribution of biological, environmental, and personal factors on the appearance of delusions in Alzheimer's disease.

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