

supranuclear palsy, which also affects this loop and in which an abnormal antero-posterior metabolic gradient has also been documented.⁸ On the other hand, lesions essentially confined to the substantia nigra, as in Parkinson's disease, do not consistently alter cortical metabolism.⁸ It is tempting to envisage dysfunction in the prefronto-striato-pallido-thalamo-prefrontal loop as one possible mechanism underlying both "athymhormia" and the abnormal anteroposterior metabolic gradient.

Mechanisms to account for the altered anteroposterior metabolic pattern in our case, other than disruption of this loop, include neuronal damage at the level of the frontal cortex. Thus although frontal atrophy was only questionable at MRI performed at the time of PET in our case, it was undoubtedly present in her two brothers at postmortem (at a much later stage of the disease), indicating frontal lobe degeneration is part of the entity. Also, the metabolic changes could reflect (and not cause) her abnormal behaviour. Thus a similar metabolic profile has been reported in patients affected by schizophrenic or affective disorders, where a flat affect and loss of drive are common features.⁹

In conclusion, however disabling this abnormal behaviour may be, it seems to be expressed as only mild anteroposterior metabolic imbalance.

Addendum

Since acceptance of this paper, the patient developed, and died from, central hypoventilation.

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Visual rating of hippocampal atrophy: correlation with volumetry

In a previous paper we described the use of visual rating of medial temporal and hippocampal atrophy as an early diagnostic marker for Alzheimer's disease.¹ Other studies on this subject have used volumetric estimations of the hippocampal complex or temporal lobe.^{2,3} These techniques are refined but time consuming. To investigate the correlation between visual rating and volumetric estimation of the hippocampus, we assessed the volume of the hippocampus in 41 subjects (20 patients with Alzheimer's disease and 21 age matched controls), of whom demographic data and MRI had been described elsewhere.¹ The volumetric assessments were carried out by one author, who had been involved in the clinical part of the previous study but had not seen the images before. He performed the analysis blinded to the diagnosis and ages of the subjects.

After magnification of the hard copies of the MRIs by projecting them on a screen with an overhead projector, the outlines of the brain and hippocampus were drawn on transparencies. Only the second to the fifth slices of each MRI were used. These transparencies were then digitalised on a Macintosh Iix with a ScanJet Iic flatbed scanner (Hewlett Packard) with a resolution of 72 dots per inch and were saved on an eight bit grey scale TIFF file (256 shades of grey). Postprocessing of the images was carried out with the public domain program IMAGE 1.35 (from W Rasband, NIH research services branch, Bethesda, Maryland, United States). The area of the hippocampus on each slice was measured and magnified by the slice thickness, thus producing an estimation of the volume. For analysis the eight volumes (four on each side) were added together and divided by four to produce a "mean total hippocampal volume".

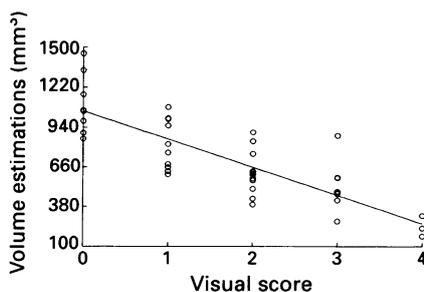


Figure Scatterplot showing correlation between visual score and volumetric estimations. The regression line is drawn in ($r = -0.83$).

The correlation between visual and volumetric assessment of hippocampal atrophy was excellent (figure; $r = -0.83$ $p < 0.001$, one-tailed).

From the figure it may be inferred that overlap occurs between some of the scores, especially between 2 and 3. Based on the volumetric assessments, it would be worthwhile to modify to a 0-2 or 0-3 scale, which would simplify the rating, but could lead to loss of discriminative power. Although drawing from magnified hard copies may introduce several measurement errors, the correlation is surprisingly high. In future research, postprocessing will be carried out on images taken directly from the scanning console, bypassing the use of hard copies.

In general, the main disadvantage of visual ratings in research settings has always been the low interobserver and intraobserver reliability.⁴ For clinical practice, however, visual ratings provide a useful and rapid assessment of hippocampal atrophy that correlates well with linear¹ and volumetric measurements and may be used to aid the clinician in diagnosing or ruling out Alzheimer's disease.

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Serum concentrations of 2',5'-oligoadenylate synthetase, neopterin, and β -glucan in patients with chronic fatigue syndrome and in patients with major depression

Chronic fatigue syndrome is characterised by debilitating severe fatigue persisting for more than six months.¹ Furthermore, it is associated with physical symptoms, such as mild fever, sore throat, arthralgia, and myalgia, as well as psychological symptoms such as headache, insomnia, depressive state, and neuropsychiatric symptoms.¹ It has often been claimed that the onset of chronic fatigue syndrome follows an infection or infection-like illness²; hence a certain microorganism(s) or virus may cause it. Another possible candidate for inducing chronic fatigue syndrome is cellular or humoral immune dysfunction, which has

been found in patients with the disease. There is controversy also as to whether or not chronic fatigue syndrome and major depression (mood disorder) represent different entities.

Mild fever, pharyngitis, and lymphadenopathy, which are suggestive of the existence of inflammation, are often associated with chronic fatigue syndrome, but the peripheral leucocyte count, erythrocyte sedimentation rate, and C-reactive protein concentration are usually normal in patients with chronic fatigue syndrome. Hence, it is possible that certain cytokines may produce the symptoms in patients with chronic fatigue syndrome and, possibly, those with major depression. For example, interferon is known to cause fever, fatigue, and psychoneurological abnormalities. We conducted this study to clarify whether or not 2',5'-oligoadenylate synthetase (2,5-AS), neopterin, adenosine deaminase, endotoxin, or β -glucan participate in the pathogenesis of chronic fatigue syndrome.

The subjects were 63 patients who fulfilled the criteria of the working definition for chronic fatigue syndrome.¹ The controls were 67 age and sex matched patients who fulfilled DSM-III-R criteria for major depression (depressive disorders). All patients with major depression and 40 healthy volunteers (recruited from hospital and laboratory staff) as normal controls completed the 30 item general health questionnaire, a screening test for psychiatric morbidity.

We found that mean (SD) serum concentrations of 2,5-AS, neopterin, and β -glucan

were significantly higher in patients with chronic fatigue syndrome (110 (10) pmol/dl, 5.8 (3.7) nmol/l, 9.5 (6.3) pg/ml, respectively) than in the normal controls (43 (13) pmol/dl, 4.1 (1.0) nmol/l, 6.1 (1.5) pg/ml respectively) ($p < 0.01$; Student's t test). Concentrations of 2,5-AS (78 (15) pmol/dl), neopterin (5.4 (2.5) nmol/l), and β -glucan (12.0 (6.4) pg/ml) were also higher in patients with major depression than in the controls (all $p < 0.01$).

The mechanism(s) for this increase is unclear at present, but the possibility of latent and prolonged infection by microorganisms(s) that are difficult to detect by ordinary laboratory tests cannot be ruled out. The raised β -glucan in the patients with chronic fatigue syndrome may have stimulated their lymphocytes to induce production of 2,5-AS and neopterin.^{2,3} It is interesting that serum 2,5-AS, neopterin, and β -glucan concentrations were also high in patients with major depression. Some researchers consider that chronic fatigue syndrome is a clearly different entity from major depression⁴; others regard the two as part of the same disease spectrum.⁵

The main reason for the second contention is that the psychoneurological symptoms found in both diseases are not distinguishable. It is well documented that treatment with interferon can be associated with fatigue and neuropsychiatric symptoms including depression. Consequently, it is conceivable that interferon induced by the mechanisms discussed may substantially contribute to the pathogenesis of chronic fatigue syndrome as well as to major

depression. This abnormal cytokine production may induce mainly physiological symptoms, depending on the underlying psychiatric and immunological state of each patient. Equally the mood disorder in both patient groups may induce these abnormalities of immunity.

Further investigations are needed to corroborate the clinical and pathogenetic relevance of the raised cytokine concentrations in patients with chronic fatigue syndrome or major depression, and to clarify the aetiology of both diseases.

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