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Clinical, psychological and neuroradiological findings in a case of chronic schizophrenia with cognitive impairment and a mis-sense mutation at codon 713 of the β amyloid precursor protein gene

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The β APP gene on chromosome 21 encodes for a protein which can be abnormally cleaved into products including the A4 peptide, which is commonly isolated from amyloid deposits in cerebral blood vessels and senile plaques in Alzheimer's disease. Mutations of codons 693, 717 and 692 have been found in hereditary cerebral hacmorrhage with amyloidosis Dutch type (Levy et al., 1990), some families with early onset Alzheimer's disease (Chartier-Harlin et al., 1991), and in a family with presenile dementia and cerebral haemorrhage (Hendricks et al., 1992), respectively.

A mutation at codon 713 in exon 17 of the β APP gene resulting in a C to T nucleotide substitution and producing an alanine to valine change, was recently described in a 63 year old woman presenting with schizophrenia and cognitive deficits (Jones et al., 1992). We present further clinical and investigative details of this case.

She first presented to the psychiatric services in 1954 with auditory hallucinations, incongruous affect, incoherent speech and disorganised behaviour. She showed a decline in functioning from 1960, with progressive social withdrawal, affective flattening, lack of motivation, and difficulty performing events in sequence. She was initially treated with ECT and had 10 courses (approximately 100 treatments) over 13 admissions. She received neuroleptics from 1964 until 1986 when a severe oro-facial dyskinesia necessitated treatment with tetrabenazine and benzhexol hydrochloride. At that time, she complained of dizzy spells and was mildly hypertensive, which has since been well controlled by diuretics.

Over the past 2–5 years she has suffered increasing memory impairment, forgetting names and recent events, repeating conversation topics and losing her way home. Her husband corroborated these memory deficits, and had noticed a step-wise deterioration. She has a family history of mental illness and neurological disease, but not of Alzheimer's disease. Maternal grandmother was schizophrenic, and brother died after a subarachnoid haemorrhage, but he did not have the APP 713 mutation (Jones et al., 1992). At age 12 she was hospitalised with tuberculosis, but had no further medical problems until hypertension was diagnosed.

On admission for investigation, mild depressive, anxious and negative symptoms were elicited. A severe oro-facial dyskinesia, lip-smacking dystonia, mild Parkinsonian tremor and bradykinesia were noted. Clinical cognitive testing revealed age disorientation and poor general knowledge, but was otherwise intact.

Detailed neuropsychological testing was undertaken. She showed a normal full-scale Wechsler Adult Intelligence Scale (WAIS) IQ of 103 (verbal IQ 107, performance IQ 97); close to the pre-

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Fig. 1. Transverse scans through the lateral ventricles. (A) SE 3565/20 proton-density weighted (PDW) image showing dilated lateral ventricles, a periventricular rim of high signal intensity, discrete high intensity lesions in both centrum semiovale and a white matter high intensity area around both occipital horns of the ventricles which extends outwards into the occipital white matter. (B) SE 3565/90 T_2 -weighted image showing similar changes as seen in the PDW image with high intensity due to CSF in dilated cortical sulci.

morbid IQ estimate of 114 from the National Adult Reading Test. Her performances on the digit symbol and digit span sub-tests of the WAIS were of average ability and above average ability, respectively, for her age. However, she scored over two standard deviations below the mean for her age on the verbal fluency (VF) task. Her score on the Rivermead Behavioural Memory Test (RBMT) was in the severely impaired range. On the Cambridge Neuropsychological Test Automated Battery, she showed marked visuo-spatial memory impairment by performance on pattern recognition and delayed matching to sample sub-tests at a level of one standard deviation below the mean. Her score on the Continuous Performance Test (CPT) indicated marked problems with response suppression. Overall, she presented with relatively preserved short-term memory (digit span) and fluid intelligence (digit symbol), in the face of severe deficits in episodic long-term memory (RBMT) and in executive functions (VF, CPT).

MRI (SE 3565/20/90), on a 1.0 Tesla scanner, demonstrated gross cerebral atrophy, marked dilatation of ventricular cisterns and fissures, and bilateral cortical surface wedge-shaped infarcts in parietal regions (see Fig. 1). Multiple high intensity signal lesions were detected throughout the cerebral white matter, a 2 mm lesion in the left cerebellar hemisphere, and a high intensity signal rim surrounded the lateral ventricles. A CT scan also showed marked global atrophy and wedge-shaped cortical infarcts. No deep white matter infarcts were identified in either scan. These findings probably reflect white matter ischaemia with interstitial oedema around the lateral ventricles.

SPET imaging was performed using 99m Tc-Exametazime to measure regional perfusion. Markedly reduced tracer uptake was found bilaterally in anterior cingulate, frontal, medial temporal, parietal and striatal regions. The average effect size was of 1–2 standard deviation units. Such a pattern is similar to that reported in Alzheimer's disease (Hunter et al., 1989).

The history is suggestive of multi-infarct dementia (MID). However, the neuropsychological results are more akin to the amnesic profile described in schizophrenia by Tamlyn et al. (1992), and to the deficits in the supervisory attentional system reported in schizophrenics by Shallice et al. (1991). Although dementing syndromes in schizophrenia generally arise early in the course of the illness, studies tend to show a deterioration in cognitive function with longer duration of the illness (Liddle and Crow, 1984).

The SPET scan results are compatible with those of Alzheimer-type dementia (Hunter et al., 1989), rather than the relative increase in fronto-parietal uptake in MID (McKeith et al., In press). The MRI findings are not compatible with MID, only superficial infarcts and generalised ischaemia being detected. High intensity lesions are a non-specific finding on MRI, but are rare in Alzheimer's disease, which reflect reduced cerebral perfusion or altered cerebral hydrodynamics (Almkvist et al., 1992). The periventricular interstitial oedema, in the absence of deep cortical infarcts, suggest an abnormality in the blood brain barrier, with a possible underlying vasculitic process.

This lady presents with a hitherto unreported constellation of clinical and investigative features. The mutation in codon 713 of the APP gene may encode for a vascular abnormality which could result in angiopathic, dementing and/or schizo-phrenic conditions; perhaps pathogenic by causing β -amyloid deposition. Our case shows some evidence of all three diagnoses and is typical of none. It is possible, given the preliminary nature of these findings and that none of 100 schizophrenic controls showed the mutation, that it is only a coincident polymorphism. Neuropathological material and genetic screening of more schizophrenics could provide a definitive answer.

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