LETTERS TO THE EDITOR

Subcortical vascular disease in elderly patients with treatment resistant depression

Failure to respond to treatment is an important and common clinical problem in the management of depressed patients. It is important, therefore, to consider this possibility before embarking on more vigorous treatments such as electroconvulsive therapy. This study reports the neuropsychological, neurological, and neuroimaging findings in patients with treatment resistant depression referred to a neurological centre for evaluation of possible underlying cerebral pathology. The aim was to ascertain the nature of clinical and neuroimaging findings in such patients, and thereby identify those features that might contribute to the recognition of cerebral pathology in elderly patients with treatment resistant depression.

The study group comprised 14 consecutive patients with treatment resistant depression referred to the cerebral function unit at Manchester Royal Infirmary over a three year period. All patients fulfilled DSM III R 1987 criteria for major depressive illness, and all had been treated with at least one type of antidepressant medication for at least three months without clinical benefit. All patients were referred by a consultant psychiatrist, and were suspected of having underlying cerebral pathology. The mean age of the patients (four men, 10 women) was 68 (SD 7-9, range 58-84) years. Eight patients were hypertensive, two had non-insulin dependent diabetes mellitus, and nine were cigarette smokers. Two had a history of cerebrovascular disease in a first degree relative. Nine had a history of depressive illness. All patients were examined by a consultant neurologist and a neuropsychologist. Profiling of cognitive deficits was obtained using a test instrument developed in this centre. Brain CT or MRI was performed on all patients, and scans were evaluated by a consultant neuroradiologist. 18F-FDG-PET was performed on all patients, and scans were evaluated by a consultant in nuclear medicine.

The table summarises the neuropsychological, neurological, structural, and functional neuroimaging findings. Neuropsychological evaluation disclosed the following features in all patients: mental slowing, difficulty on tasks involving manipulation of information (such as reversal of months of the year and mental calculation), difficulty in motor sequencing tasks, perseveration, failure in tests sensitive to "frontal lobe" dysfunction, and memory impairment suggestive of retrieval and organisational failures. Neurological signs were elicited in 10 patients. Of these, seven had slow and restricted eye movements, five were dysarthric, seven had focal upper motor neuron deficits (pyramidal weakness, pathologically brisk reflexes, or extensor plantar response), five had signs of akinesia, rigidity or tremor, four had a gait disorder, and three exhibited frontal lobe release phenomena. Neurological examination was normal in four patients. Brain CT was reported as abnormal in seven patients. Of these scans, three showed areas of low attenuation in subcortical regions and four showed evidence of cerebral atrophy. Of the six patients in whom CT images were reported as "normal", two subsequently had MRI performed. These scans disclosed extensive subcortical vascular pathology in both cases. 18F-FDG-PET images were reported as abnormal in nine patients. Cerebral blood flow (CBF) abnormalities were either generalised or predominantly anterior in distribution in eight cases; CBF SPECT images were reported as normal in five patients. In summary, all 14 study patients showed patterns of neuropsychological breakdown indicative of subcortical dysfunction and 10 patients showed at least two components of a neurological syndrome characteristic of subcortical vascular pathology. Brain CT showed changes consistent with subcortical vascular pathology in three patients and MRI showed evidence of sub-

Summary of neuropsychological, neurological, and neuroimaging findings in fourteen patients with treatment resistant depression

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Neuropsychological findings</th>
<th>Neurological signs</th>
<th>CT</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subcortical dysfunction</td>
<td>None</td>
<td>Subcortical changes</td>
<td>Anterior cerebral abnormality</td>
</tr>
<tr>
<td>2</td>
<td>Subcortical dysfunction</td>
<td>Eye movement disorder, Gait disorder, Frontal lobe phenomena</td>
<td>Subcortical changes</td>
<td>Generalised cerebral abnormality</td>
</tr>
<tr>
<td>3</td>
<td>Subcortical dysfunction</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Subcortical dysfunction</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>Subcortical dysfunction</td>
<td>Eye movement disorder, Dysarthria, Akinesia/rigidity</td>
<td>Normal</td>
<td>Anterior cerebral abnormality</td>
</tr>
<tr>
<td>6</td>
<td>Subcortical dysfunction</td>
<td>Eye movement disorder, UMN signs, Tremor</td>
<td>Generalised cerebral atrophy</td>
<td>Posterior cerebral abnormality</td>
</tr>
<tr>
<td>7</td>
<td>Subcortical dysfunction</td>
<td>Dysarthria, UMN signs, Tremor, Gait disorder</td>
<td>Anterior cerebral atrophy</td>
<td>Normal</td>
</tr>
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<td>8</td>
<td>Subcortical dysfunction</td>
<td>UMN signs, Gait disorder</td>
<td>Subcortical changes</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Subcortical dysfunction</td>
<td>Dysarthria, UMN signs, Frontal lobe phenomena</td>
<td>Generalised cerebral atrophy</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>Subcortical dysfunction</td>
<td>Eye movement disorder, Dysarthria, Gait disorder</td>
<td>Subcortical changes</td>
<td>Generalised cerebral abnormality</td>
</tr>
<tr>
<td>11</td>
<td>Subcortical dysfunction</td>
<td>Akinesia/rigidity, Gait disorder</td>
<td>Generalised cerebral atrophy</td>
<td>Anterior cerebral abnormality</td>
</tr>
<tr>
<td>12</td>
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<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>Subcortical dysfunction</td>
<td>Eye movement disorder, Dysarthria, Frontal lobe phenomena</td>
<td>CT Normal, MRI subcortical changes</td>
<td>Normal</td>
</tr>
<tr>
<td>14</td>
<td>Subcortical dysfunction</td>
<td>Eye movement disorder, Dysarthria, Akinesia/rigidity</td>
<td>CT Normal, MRI Subcortical changes</td>
<td>Normal</td>
</tr>
</tbody>
</table>

UMN = Upper motor neuron.
Hereditary transcobalamin II deficiency: a 22 year follow up

Transcobalamin II (TCII) is the major plasma transport protein for vitamin B12. Its gene has been localised to chromosome 22.1

Genomic structure suggests that it, the other cobalamin transporters TCII and TCIII, and gastric intrinsic factor originated by duplication of an ancestral gene.2 Inherited deficiency of TCII leads to reduced delivery of vitamin B12 to the tissues and to its impaired absorption from the ileum. We reported a patient with hereditary TCII deficiency with neurological involvement in 1986 and have recently re-examined him. He had spastic paraparesis and unrelated parents. A brother had died aged 6 months with peripheral pancytopenia and a megaloblastic bone marrow. The patient developed neurological features in the neonatal period and was found to have a megaloblastic anaemia. He was diagnosed as having dihydrofolate reductase deficiency3 and was started on parenteral treatment with folinic (5-formyltetrahydrofolate) acid. When aged 6 months he was stated to have had normal mental and physical development. He continued to receive daily injections of folinic acid but from the age of 12 months his mental and motor development was delayed. When examined in London at the age of 2 years he was unable to sit or stand unsupported and there was jerky ataxia of the upper limbs. His tendon reflexes were depressed and both plantar responses were extensor. Frequent spontaneous attacks occurred in which he became transiently rigid and unresponsive. Reinvestigation showed normal hepatic function with absent vitamin B12 binding to serum TCII. Folic acid treatment was discontinued and he was started on thrice weekly injections of 1000 mg folic acid. Clinically and neurologically he improved. When reviewed in 1980 his intellectual development was still severely reduced. He walked unsteadily with assistance and both feet in an equinus position. Neurological examination showed microcephaly and bilateral pyramidal signs with extensor plantar responses. All his tendon reflexes were absent and from the ankle jerks. He has been reviewed again in June 1996 when, after further improvement, his condition had stabilised. His peripheral blood count was normal. He had been experiencing grand mal seizures at about 2-year intervals but these had ceased after an increase in the dosage of sodium valproate. Speech utterance was limited and restricted to single words. Speech comprehension was reasonable. Tongue movements were sluggish. Upper limb muscle strength was good but discrete finger movements were sluggish. There was no upper limb ataxia. There was increased tone in both legs with moderate weakness of upper motor neuron distribution. He walked with a spastic "scissors" gait with his feet in equinus. His tendon reflexes were generally brisk and both plantar responses were extensor. Adequate sensory testing was not possible.

An EEG was of low medium voltage with somewhat discontinuous 10–12 Hz central and postcentral rhythmic activity and low voltage beta activity. A single burst of bilateral but predominantly right sided 2.5–4 Hz waves was recorded. Brain MRI with T2 weighted axial sequences showed reduced volume of the cerebellum in particular, of the corpus callosum which was diffusely thinned. There was hyperintensity of the FLAIR sequence in the immediate periventricular white matter and in the subcortical white matter. No other frontal or temporal changes. Imaging of the brainstem and cerebellum was normal.

Except for two possible instances, neurological dysfunction has not been present at the time of haematological presentation of hereditary TCII deficiency in the cases reported to date but has appeared later. The clinical features resulting from vitamin B12 deficiency in infancy seem to differ from those that occur when deficiency develops in later life. In the present case, in a child reported by Burman et al.,4 and in a child reported by Rozman et al.5 the neurological syndrome was dominated by CNS changes that included microcephaly, generalised epilepsy, impaired cognitive development, emotional lability, and dystonia because of ataxia and spastic lower limb weakness. Sensory neuropathy was not a feature. Motor and sensory nerve conduction studies were normal in our case in 1980 and were not repeated at the recent review.

It is vital that hereditary TCII deficiency should be recognised promptly so that treatment with vitamin B12 can be initiated to avoid irreversible central nervous system damage. In the present case diagnosis and appropriate treatment were unfortunately delayed. Comparison of the patient's present state with that in 1976 and 1985 indicates that although neurological improvement has occurred but he remains with severe cognitive impairment, controlled epilepsy, poor manual function, and a spastic gait. The possible mechanisms for central nervous system dysfunction related to B12 deficiency have recently been reviewed.6 The mechanism of B12 uptake into the CNS is not established but cobalamin receptors could be present on brain capillaries and choroid plexus as well as on tumour cells. TCII is known to be present in the CSF and it has been shown that TCII is synthesised by astrocytes.7 Astrocytes may possibly be involved in cobalamin recycling and transport in the CNS.

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