Progressive loss of speech output and orofacial dyspraxia associated with frontal lobe hypometabolism

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Abstract
Three patients are described with slowly progressive loss of speech and dysarthria associated with orofacial dyspraxia, initially with intact written language, who subsequently developed more widespread cognitive abnormalities. Positron emission tomography (PET) revealed bifrontal hypometabolism in all of the patients, most marked in the inferior and lateral portions of both frontal lobes, with some extension into the parietal and temporal cortices in one case. These patients may represent a further example of focal progressive cortical degeneration.

Progressive neuropsychological deficits due to focal cortical degeneration have been described by a number of authors. These deficits include dysphasia,\(^1\) dyspraxia or agnosia,\(^2\) and cortical blindness.\(^3\) Most of the cases reported in the literature refer to progressive language-related difficulties, some of which eventually progress to more generalised cognitive deterioration.\(^4\) More generalised cortical degenerations may also present with language difficulties, for example Alzheimer’s disease (AD),\(^5,6\) Pick’s disease,\(^7\) and the so-called frontal lobe dementias.\(^8,9\) Typically, these degenerative disorders are associated with word retrieval difficulties, paraphasias, or dysgraphia. Dysarthria with orofacial dyspraxia has not been generally recognised as a feature of a degenerative dementia, although it may occur in the context of vascular and traumatic lesions of the frontal lobes. Three patients are reported with progressive loss of speech, initially with intact written language, who subsequently developed a more widespread intellectual deficit. All had marked orofacial dyspraxia as an initial presentation. Neuropsychological and PET studies were performed in an attempt to delineate more clearly the neuropsychological and neuroanatomical correlates of this unusual clinical condition.

Case 1
A 64 year old housewife presented with a three year history of progressive speech production difficulty. One year after the onset of symptoms, her speech was noted to be effortful, with phonemic paraphasic errors, but her repetition of words was relatively satisfactory. Two years later, on assessment before PET scan, her understanding of speech remained well preserved, but her speech expression had deteriorated further. She was dysarthric, and her verbal output was limited to one or two words. In spontaneous writing, she made occasional grammatical errors, and when writing to dictation she transposed or omitted some words. She had marked orofacial apraxia, with an inability to yawn, blow out a match, or blow a kiss on request. When asked to cough, she would only say the word “cough”, but was able to do so spontaneously. By contrast, she was able to copy gestures and to mime acts correctly, apart from using the flat of her hand when asked to pretend to comb her hair. Tongue movements were normal, and there were no primitive reflexes. General neurological examination was normal, as was general examination, with a blood pressure of 150/90 mm Hg. All haematological and biochemical investigations were normal, including thyroid function tests. Electroencephalography (EEG) was also normal, but a computerised tomography (CT) scan showed left frontal and anterior temporal atrophy (fig 1).

Neuropsychological assessment was performed on three occasions. In her first assessment (August 1987) on the Wechsler Adult Intelligence Scale (WAIS),\(^10\) she achieved a verbal IQ of 95 and a performance IQ of 108. These scores did not suggest any significant degree of general intellectual deterioration, her lower verbal IQ being mainly due to her speech impairment.

Figure 1. CT head scan of patient 1. The left hand side of the head is seen on the right of the image.
production difficulties. On the Graded Naming Test\textsuperscript{11} and the Naming from Description Test\textsuperscript{12} she scored 12/30 and 12/15 respectively, suggesting only mild inefficiency on naming tasks. On a spelling test she performed well (Baxter test\textsuperscript{13}). Her performance on tests of visual perception and visuospatial function was satisfactory, with a score of 17/20 on the Unusual Views test\textsuperscript{6} and 20/20 on the Dot Centre test.\textsuperscript{14} There was no unequivocal evidence of memory impairment: she named 6/12 Famous Faces and recognised another three (results within normal range for her age group), and achieved a perfect score (30/30) on the “Camden A” Recognition Memory Test comprising coloured photographs (Warrington, personal communication). Although on the longer Recognition Memory Test\textsuperscript{14} her performance was weak, scoring only 34/50 for words and 38/50 for faces, this appeared to be secondary to attentional factors. On two tests of frontal lobe function she performed satisfactorily: she completed the Weigh! Swag! Task\textsuperscript{7} and her responses on the Cognitive Estimates Test\textsuperscript{15} were within normal limits. On retesting in January 1989, her verbal IQ was 88 and her performance IQ 97, indicating a relatively mild but significant deterioration since her previous assessment on general ability tests. Despite her speech production difficulties noted earlier her repetition skills remained relatively well preserved. Her naming skills were thought to be slightly weaker than previously, scoring 9/30 on the Graded Naming Test and 13/15 on the Naming Test.\textsuperscript{16} There was no suggestion, however, of comprehension difficulties. Her perceptual skills had remained satisfactory, and on this occasion she scored 40/50 on both the verbal and visual versions of the Recognition Memory Test, that is within the average range.

In the most recent assessment at the time of PET scanning (July 1989), a further deterioration in her verbal skills was observed. Verbal IQ was now 92, but performance IQ remained at 97. Consistent with the latter was her average score (6/12) on Advanced Progressive Matrices Set 1.\textsuperscript{17} There appeared to be no significant change in her speech production/articulatory skills since her previous assessment. On the Oldfield Naming Test\textsuperscript{20} she scored 21/30 which was in keeping with her previous performance on the Graded Naming Test. Word comprehension ability appeared to be well preserved, with a score of 134/150 on the British Picture Vocabulary Scale.\textsuperscript{18} On the Unusual Views test of visual perception she scored 20/20. She achieved an average score on the verbal part of the Recognition Memory Test (42/50) but on the visual part she performed below the fifth percentile (35/50), apparently due to lapses in concentration. Thus on a shorter visual recognition memory test comprising coloured photographs of buildings (Warrington, personal communication) she obtained a perfect score (25/25).

In summary, over a period of two years her verbal skills had deteriorated significantly and there was also evidence of a mild decline in her nonverbal reasoning skills. Her memory and perceptual functions were generally well preserved. Her speech continued to be effortful and dysarthric with phonemic paraphasic errors. Word comprehension and literacy skills had remained intact, but there was evidence of mild word retrieval difficulties.

**Case 2**

A 65 year old right handed retired engineering technician presented with a six year history of speech disturbance. The initial symptoms had been a reduction in verbal output, with stuttering, although his writing remained normal. He had a past history of exertional angina, but no other history of note. There was no family history of dementia or other neurological illness. Eighteen months after the onset of symptoms, he had non-fluent, dysarthric speech, with evidence of orofacial dyspraxia. Verbal comprehension and confrontational naming were excellent (allowance was made for his impaired speech production). Spontaneous speech was dysfluency, with agrammatism, perseveration, construction and choice of vocabulary. His symptoms progressed, however, and when assessed before PET scan, was described by his family as having been mute for three years. Verbal comprehension remained well-preserved, but his writing was dysgraphic, and agrammatic. In addition, his non-verbal communication seemed to be impaired, with lack of eye contact, and difficulty in understanding gestures. He had marked orofacial dyspraxia, and was unable to cough, yawn or blow a kiss on command. His conduction and repetition skills had also been impaired. He was slightly slow. He was able to cough spontaneously. In contrast, he was able to copy hand gestures, and perform transitive and intransitive mimes. Pout and snout reflexes were present, and he demonstrated “magnetic” behaviour with forced utilisation. General and neurological examination was otherwise normal, with a blood pressure of 110/60 mm mercury. All haematological and biochemical investigations were normal, including thyroid function tests. His CSF was acellular with a total protein content of 0.86 g/l, the syphilis serology was negative, and no oligoclonal bands were detected. EEG was normal, but a CT scan showed frontal and anterior temporal atrophy (fig 2).

Neuropsychological testing was carried out on two occasions, four years apart. On first assessment (November 1984), he achieved a performance IQ of 123. He could comply with the demands of only three verbal subtests of the scale because of his speech production deficit, but on all of them he scored within the average range or above. On the verbal and visual versions of the Recognition Memory Test, he performed at a bright average level or above (Words 48/50 correct, Faces 44/50), and on the Unusual Views test of visual perception he scored 20/20. As noted above he presented with severe speech production deficit. He had difficulty with the repetition of single words, and his repetition of single phonemes was particularly impaired. By contrast, his naming to confrontation and word comprehension skills were very well preserved, scoring 27/30 on the Graded Naming Test and 145/150 on
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Case 3
A 65 year old retired bank messenger presented with a three year history of difficulty in speaking and swallowing. He took early retirement one year before the onset of symptoms, and had attributed this to his inability to continue with his work after a bereavement in the family. The symptoms may have started after a social occasion when he had had to meet some of his ex-colleagues: his wife noticed that he had been extremely anxious about the occasion beforehand. On his return home, his speech was slurred for the first time, despite having drunk very little alcohol, and it did not return to normal. His speech progressively deteriorated, although until one year before presentation, he was able to communicate effectively by means of written messages. Soon after the onset of the speech disturbance, he also complained of swallowing difficulties, particularly for liquids. There was no nasal regurgitation. He continued to drive a car without getting lost, and recognised familiar faces without difficulty. On first assessment six months before the PET scan, and again four months later, his speech was hypophonic and dysarthric. Verbal comprehension appeared to be somewhat impaired, although he was able to follow a three stage command. Orofacial dyspraxia was present, with inability to cough, yawn, or blow a kiss on command, although he was able to cough spontaneously. In addition, he was unable to hold his breath, despite understanding the instruction. Dyspraxia of the limbs was also noted, with inability to copy some relatively complex hand movements, and use of body parts while miming. The rest of the neurological examination was normal, with no muscle wasting or fasciculation, normal symmetrical reflexes, and flexor plantar responses. General examination was also normal, with a blood pressure of 150/90 mm Hg. On later assessment, at the time of the PET scan, there had been further deterioration of his speech, which was barely intelligible. Grasp, pout and snout reflexes were now present, with a brisk jaw-jerk. Swallowing water induced choking. On general neurological examination, muscles were noted to be generally wasted, and he had developed scattered fasciculation and extensor plantar responses. Limb tone and power were normal, and reflexes symmetrical. Haematological and biochemical investigations were normal as was CSF examination, with negative syphilis serology. EEG, CT head scan (fig 3) and carotid angiography were all normal. Electromyography showed fasciculation with fibrillation, and sharp waves in upper and lower limbs, consistent with anterior horn cell disease.

Neuropsychological assessment was performed on two occasions, six months apart. His score on the National Adult Reading Test suggested a premorbid IQ of 105. In his first assessment, he achieved a verbal IQ of 71, and a performance IQ of 87. His score on Raven's Coloured Progressive Matrices was at the twenty fifth percentile. These results indicated a general intellectual deterioration, particularly with verbal tests. His articulatory impairment appeared to be a specific deficit in producing the basic sounds of speech correctly by making distortions of target phonemes. However, on the Oldfield and Graded Naming Tests he scored 20/30 and 10/30 respectively, suggesting only mild word retrieval difficulties, and on the Peabody Picture Vocabulary Test scored at
Figure 3 CT head scan of patient 3. The left hand side of the head is seen on the right of the image.

Methods

$^{18}$O steady state PET scans were performed on the CTI/931/12/8 (CTI, Tenn, USA) scanner at the MRC Cyclotron Unit at the Ham- mersmith Hospital, to obtain regional values of CMRO$_2$ (cerebral metabolic rate for oxygen). The performance characteristics of this scanner have been described. Ethical approval for these studies, and for normal studies on eight volunteers (aged 59–83) mean age 69.25 years, was obtained from the Ethical Committees of St Mary’s, the National and Hammersmith Hospitals. Approval for administering radio-labelled gases was obtained from ARSAC (Administration of Radioactive Substances Advisory Committee of the United Kingdom). Written consent was obtained from all patients, and normal volunteers, after a full explanation of the procedure. The details of the control groups are described elsewhere.

Patients and subjects were positioned on the scanning bed, with the head symmetrically aligned along the orbitomeatal line, resting in an individually made rigid polyurethane foam head mould. Careful observation of the patients and subjects throughout the scan ensured that there was no significant head movement. A 22 gauge plastic cannula was inserted into the radial artery at the wrist, after subcutaneous infiltration of long acting local anaesthetic (bupivacaine 1%). After a 15 minute transmission scan (Ge$^{68}$Ga$^{68}$), two consecutive emission scans were performed during inhalation of C$^{18}$O$_2$ and C$^{18}$O$_2$ respectively, at steady state, with a ten minute wash-out period between each scan. Finally, a further six minute scan following four minutes of C$^{18}$O$_2$ inhalation, and equilibration for one minute, was collected. The emission scans were transformed into parametric images after correction for attenuation, using the arterial oxygen content and whole blood and plasma activities, measured in triplicate, during C$^{18}$O$_2$, C$^{18}$O$_2$, and C$^{15}$O scanning. Thus four quantitative data sets of CMRO$_2$, CBF (cerebral blood flow), and OER (oxygen extraction ratio), and cerebral blood volume (CBV) were obtained. Details of this method, and the cerebral blood volume component, have been described previously.

Images were inspected to ascertain the presence and position of the focal deficits. Images were presented as 15 planes of data with a resolution of $8.5 \times 8.5 \times 7$ mm after reconstruction, with no interplane deadspace. Images were also inspected in the coronal and sagittal planes following a 1:3 linear interpolation in the vertical axis (z-plane), thus generating 43 images. Scans were analysed on a computer (Sun 3/60) with image analysis software (ANALYZE:BRU/Mayo Clinic), which allows scans to be displayed relative to the intercommissural line (AC-PC line). This permitted anatomical localisation using standard stereotactic coordinates based on the Talairach atlas.

Numerical data were obtained using a circular region of interest of diameter 8 mm (approximately one resolution element), which covered the visible cortical ribbon. In each a level equivalent to an IQ of 77. His spelling on the Baxter test was within the normal range. His recall of major events was satisfactory, but on two recognition memory tests comprising coloured photographs (Warrington, personal communication) he scored at a defective level (Camden A: 24/30, Camden B 14/30). His bimanual hand coordination was poor, and he had difficulty completing the Weigl’s Sorting Test. Visual perception appeared normal as he scored 19/20 on the Fragmented Letters Test. Thus at this stage he had a marked speech production deficit with only mild word retrieval difficulties per se, in the context of general intellectual deterioration; there was evidence of impairment on some memory tests but his visual perceptual skills were intact. He was reassessed six months later, at the time of the PET scan. He attempted to talk, but could only produce undifferentiated sounds. His writing ability was impaired, with spelling errors and occasional neologisms. On the British Picture Vocabulary Test, he scored only 44/60, that is, below the first percentile. On the verbal and visual versions of the Recognition Memory Test he performed below normal limits (Words 37/50, Faces 23/50), although he was able to identify 10/15 Famous Faces. His performance IQ on the WAIS had deteriorated to 67, and his score on the Raven’s Coloured Progressive Matrices was now below the fifth percentile. Tests of visual perception also showed impairment, with a dull average score on the Objects Silhouettes test of visual perception, and a defective level score on the animals version of this test. Qualitative aspects of his behaviour during testing suggested a tendency to perseveration, which appeared to have affected his performance on certain tests. In summary, the patient’s ability to communicate verbally had become very severely impaired, and his comprehension and writing skills had also become very limited. His language deficits were mirrored by a further deterioration in his reasoning skills.
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Table. This shows the CMRO₂ values for each of the patients for each of the anatomical areas sampled, on both sides of the brain. Mean (SD) values for the normal population, are also given. Patient values marked with an asterisk (*) are outside the 95% confidence interval.

<table>
<thead>
<tr>
<th>Normal Subjects (n = 8)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>2.88 (0.41)</td>
<td>2.91 (0.44)</td>
<td>2.06 (1.66)</td>
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<tr>
<td>Anterior Frontal Gyrus (F1)</td>
<td>2.92 (0.27)</td>
<td>2.96 (0.36)</td>
<td>1.96* (1.29)</td>
</tr>
<tr>
<td>Middle Frontal Gyrus (F2)</td>
<td>2.66 (0.31)</td>
<td>2.66 (0.31)</td>
<td>1.73* (1.20)</td>
</tr>
<tr>
<td>Posterior Frontal Gyrus (F3)</td>
<td>2.67 (0.37)</td>
<td>2.73 (0.37)</td>
<td>0.96* (0.30)</td>
</tr>
<tr>
<td>Superior Temporal Gyrus (T1)</td>
<td>2.74 (0.40)</td>
<td>2.76 (0.41)</td>
<td>2.31 (1.57)</td>
</tr>
<tr>
<td>Middle Temporal Gyrus (T2)</td>
<td>2.78 (0.42)</td>
<td>2.79 (0.42)</td>
<td>2.31 (1.57)</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus (T3)</td>
<td>2.81 (0.40)</td>
<td>2.82 (0.42)</td>
<td>2.31 (1.57)</td>
</tr>
<tr>
<td>Anterior Parietal Cortex</td>
<td>2.82 (0.42)</td>
<td>2.83 (0.41)</td>
<td>2.04 (1.26)</td>
</tr>
<tr>
<td>Posterior Parietal Cortex</td>
<td>2.85 (0.40)</td>
<td>2.85 (0.41)</td>
<td>2.31 (1.57)</td>
</tr>
<tr>
<td>Occipital Cortex</td>
<td>3.49 (0.62)</td>
<td>3.43 (0.61)</td>
<td>2.76 (2.96)</td>
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<td>Cerebellum</td>
<td>3.72 (0.43)</td>
<td>3.64 (0.55)</td>
<td>2.90 (2.93)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.47 (0.58)</td>
<td>3.49 (0.61)</td>
<td>2.39 (2.59)</td>
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<tr>
<td>Caudate Nucleus</td>
<td>3.55 (0.63)</td>
<td>3.58 (0.62)</td>
<td>3.38 (3.07)</td>
</tr>
<tr>
<td>Putamen</td>
<td>3.52 (0.66)</td>
<td>3.54 (0.65)</td>
<td>2.60 (3.14)</td>
</tr>
</tbody>
</table>

Values marked * are outside 95% confidence interval, that is p < 0.05.

Results
CMRO₂ results for the three patients, and the eight normal volunteers, are shown in the table. CMRO₂ was matched in all regions with CBF, with a normal OER. Scans from all patients, with a normal for comparison, are shown in Fig 4. Regional CMRO₂ values are illustrated graphically in Fig 5.

The results show a profound reduction in frontal lobe metabolism in all cases, affecting particularly the inferior and middle frontal gyri on both sides. In Case 2, where there was a longer history and the most severe symptoms, there was also extension into the parietal and temporal lobes on the right. Cases 1 and 3 had cortical hypometabolism restricted to both frontal lobes, particularly to the posterior frontal gyrus. In Case 3, low metabolism was also found in the left thalamus and left caudate nucleus, while metabolism in the putamen appeared to be normal.

Discussion
The association of loss of speech output and orofacial dyspraxia with frontal lobe lesions, affecting particularly the inferior and lateral portions of the frontal lobes, is in keeping with data from studies of patients with vascular lesions that have implicated the left inferior frontal lobe in the articulation of speech.³⁵ Orfacial dyspraxia appears to be a frequent accompaniment of these lesions. A number of cases of dysarthria associated with orofacial dyspraxia due to missile injury to the left frontotemporal region, were described by Nathan,³⁶ who used the term “cortical dysarthria” to describe loss of speech output in the presence of relatively preserved written language in these cases. Recently, three patients with permanent mutism, but completely intact written language and gestural communication, two due to trauma, and one due to bilateral vascular lesions, have been reported.³⁷ In all cases, orofacial apraxia was also a very prominent feature, and CT scans showed bilateral low density lesions in the fronto-temporal lobes. The authors suggest that bilateral frontal dysfunction is necessary for permanent mutism with orofacial apraxia. This inference agrees with the PET data presented here.

Although the underlying etiology in our three cases is unknown, the slowly progressive
history in normotensive patients, and the absence of vascular lesions on CT scan, make a degenerative aetiology likely. In all these patients, the deficits had initially been limited to speech production, in the absence of any other specific language impairment. However, all the patients had deteriorated before scanning, so that widespread but not global, intellectual deterioration was present. These cases therefore seem to represent a slowly progressive cognitive disorder, apparently arising from a focal cortical degeneration, and eventually progressing to a more generalised intellectual deterioration.

Focal cortical degeneration has been described as a cause of progressive dysphasia, apraxia, agnosia, and visual agnosia. Progressive loss of speech output with orofacial dyspraxia due to a degenerative cortical process of the frontal lobe has not previously been described. Rossor et al (paper submitted) described frontal lobe hypometabolism in association with progressive upper limb dyspraxia and gait disturbance, but in their three cases speech was not affected. In the two patients who had PET scans, frontal lobe hypometabolism was most marked in the midline anterior frontal region, in contrast to the more posterior and lateral frontal hypometabolism in our cases.

The underlying histopathology in progressive focal cortical degeneration may be heterogeneous. One case of a patient with progressive aphasia who subsequently became demented was found at necropsy to have Pick’s disease, another had the pathological features of Alzheimer’s disease, while yet another had Creutzfeldt-Jakob disease. Two further cases, who had aphasia without more generalised dementia, were found to have spongiform change localised to the left fronto-temporal region.

Frontal lobe hypometabolism has been reported in dementia of the frontal lobe type and in Pick’s disease. Dysphasia is reported in Pick’s disease, but not in isolation from other cognitive abnormalities or personality change. Of the frontal lobe dementias, in the series reported by Gustafson all the patients developed language abnormalities, but these were limited to stereotyped phrases, echolalia, verbal mannerisms and confabulation, rather than speech production abnormalities. Similarly, and unlike our patients, in the seven frontal lobe dementia cases reported by Neary et al, speech production deficits were not a prominent early feature, although reduction in verbal output with stereotyped phrases and paraphasias occurred later in the disease. None of our cases fit the classic description of Pick’s disease, although the presence of progressive frontal hypometabolism associated with the development of more widespread intellectual deficits raises this as a possibility.

Case 3 differs from Cases 1 and 2 in two respects, namely the prominent swallowing difficulty and the presence of muscle wasting and fasciculation. Dysphagia may be associated with unilateral or bifrontal lobe lesions, and in this patient preceded the appearance of the clinical features of motor neuron disease (MND) by some three years. MND may rarely be associated with cortical disease, and a frontal lobe dementia characterised pathologically by neuronal loss and spongiform change has been described. A case of MND associated with dementia has recently also been reported in which extensive neuronal loss and gliosis of the thalamus was found at necropsy. It is noteworthy that in case 3, CMRO₂ in the left thalamus and left caudate nucleus was low; this patient had a three year history of orofacial dyspraxia with anterior horn cell features occurring only very late in the disease. The
underlying histology in our patients remains unknown and compared with reported necropsy cases of focal cortical degeneration—40—45 may be heterogeneous. These cases, however, present a clinically recognisable syndrome which seems to represent a further example of focal cortical degeneration.

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