Brain glucose utilisation in a patient with "athymhormia" from a family with autosomal dominant parkinsonism and psychic disturbances

Recently, we reported1 a family with a picture clinically and neuropathologically consistent with the syndrome of autosomal dominant parkinsonism associated with psychic disturbances (ADPPD).2

The psychic disturbances reported in patients with ADPPD have remained ill defined to date, but have often been referred to as “mental depression” or “apathy.” In one patient from our family with ADPPD, one patient was able to further qualify these psychic features, and to assess the underlying brain functional alterations with PET.

In 1987 a 56 year old female patient showed progressive psychic retardation. In 1989 she showed global hypokinesia with slight extrapyramidal hypotonia but no tremor. At that time, a course of levodopa treatment was begun but had to be stopped because of total digestive intolerance. In 1990, akinesia was pronounced but extrapyramidal hypotonia was still moderate. Meanwhile, the patient had become more and more indifferent to her surroundings, neglecting everyday chores and dependent for everyday matters on those attending her. She had no complaints except that of being mentally void. She exhibited a flat affect but no anxiety, and did not express any depressive thoughts. She was, however, reluctant to submit to medical examination. In addition to akinesia, examination highlighted an inexpressive face. The extrapyramidal hypotonia of all four limbs without axial hypotonia; examination at a date close to PET showed resting tremor of the lower limbs. There was no oculomotor abnormality.

Two years after onset the neuropsychological testing (limited by the patient’s lack of cooperation) showed no significant global intellectual deterioration (Benton’s visual retention test, Stroop’s cognitive assessment set T = 76, mini mental state T = 28), although her memory quotient on the Wechsler memory scale was slightly low at 86. Verbal fluency was reduced at six words a minute and the verb span was reduced slightly at five. No sign of frontal lobe dysfunction could be elicited on Luria’s graphic series. There was no grasp reflex. Brain CT, EEG, and computer tomography were all normal. Questionable global frontal atrophy could be seen on T1 and T2 weighted MRI performed in 1990.

Her two brothers and her only sister had a similar clinical presentation. Postmortem examination on the two brothers (carried out six and 18 years after the onset of the illness) had shown essentially identical lesions: cortical atrophy limited to the frontal lobes, massive neuronal and pigment loss in the substantia nigra and other brainstem pigmented nuclei, and moderate neuronal loss in the striatum, pallidum, thalamic nuclei, septal nuclei, and diagonal band of Broca. No Lewy body was found by optical microscopy or immunocytochemical staining with ubiquitine antibodies either in the substantia nigra or in the cortex. Immunocytochemical staining by A4 protein and TAU protein antibodies were negative. No senile plaques, neurofibrillary degeneration, amyloid angiopathy, Pick’s bodies, or iron deposition were found.

In 1990, the cerebral utilisation of glucose (CMRg) was studied at rest with eyes closed, by means of 18-fluorodeoxyglucose, with a seven slice PET device of high resolution (5.5 x 5.5 x 5.9 mm, x, y, z model TTV 03, LETI, Grenoble, France) in stereotaxic positioning conditions relative to the Glabellina-Line ion. Attenuation correction was carried out by means of a transmission scan. The regions of interest were positioned directly over the MRI cross sections corresponding to the PET planes, by means of a software enabling MRI data acquired in 3D (FLASH procedure) to be resliced to the PET coordinates with respect to the Glabellina-Line landmark.

Anatomical structures were identified on the MRI relative to the bicommisural line, and with Talairach’s stereotaxic atlas of the human brain. The circular (14 mm diameter) regions of interest, 116 in number, aimed at analysing the main functional neocortical and subcortical structures, with averaging over both sides.

The absolute CMRg values and the relative metabolic indices (region/neocortex) were compared with confidence intervals calculated in a sample of 10 healthy volunteers of mean age 51 (SD 9) years. The confidence intervals for single subject predictions were calculated as mean (SDt), adjusting t to the sample size and the two tailed probability value chosen (t = 2.262 for 9 df, and p < 0.05 here).

Analysis of the absolute CMRg values showed no significant abnormality, although the values for all the structures were close to the lower 95% confidence limit as calculated in our control group. Analysis of the “Region/neocortex” indices (table) showed diminished values for the lateral prefrontal cortex, which just reached the p = 0.05 level. The temporal/neocortex index was significantly reduced (p < 0.05), and the occipital/neocortex index was significantly raised (p < 0.01); other regional metabolic indices showed no significant change. A lateral-prefrontal/occipital ratio, calculated to confirm the anteroposterior metabolic gradient, was significantly (p < 0.05) reduced (0.78-7.95 for a 95% lower confidence limit of 0.80).

Our patient’s abnormal behaviour comes nearest to what has been described since the 1920s in the French literature as “athymhormia” (in Greek, lack of thyrox, affect and thyrox, drive), initially in psychotic patients and more recently in patients with bilateral lesions of the striatum.3 Laplante et al4 described a similar presentation in patients with bilateral lesions of the pallidum or frontal cortex in which they called “loss of psychic self-activation” or “psychic akinesia,” also described recently after paramedian bilateralthalamic infarct.5 Both “athymhormia” and “loss of psychic self-activation” share certain features that suggest frontal lobe dysfunction (for example, mental retardation, reduced initiative), but their hallmark is loss of drive (lack of interest in things of life) and a flat affect (lack of emotional reaction), with no indication of mental deterioration. Reversal of this behaviour by external stimulation, however, seems less efficient in “athymhormia,”5 which was the case in our patient.

The cerebral metabolic values in our patient showed minor changes, with a marginally significant relative lateral-prefrontal, and significant lateral-temporal hypometabolism, as well as a significant increase in relative metabolism of the occipital cortex, but without metabolic alterations of the precen- tral cortex or parietal lobe. This pattern suggests an abnormal anteroposterior metabolic gradient, also shown by a significantly reduced lateral-prefrontal/occipital ratio. Because this is the first report of metabolic changes in the brain in ADPPD, our find- ings can only be compared with previous literature in other related diseases.

Previous studies in patients with psychic akinesia from mainly bipallidal or bithalamic lesions have also reported mild lateral prefrontal hypometabolism, suggesting disruption in the prefronto-striato-pallido-thalamo-prefrontal circuit7 at different levels results in a similar clinicometabolic picture. Neuropathological data in our patient’s two brothers (obtained at an advanced stage) indicate the presence of lesions at several locations in this circuit, with a possible cumulative effect on cortical function; moreover, this loop was presumably deprived of its modulating dopaminergic afferents, as is also the case in progressive

<table>
<thead>
<tr>
<th>Regional metabolic ratios (region/neocortex)</th>
<th>Region</th>
<th>Patient</th>
<th>Controls (mean (95% confidence intervals))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontobasal cortex</td>
<td>0.91</td>
<td>0.94 (0.73-1.15)</td>
<td></td>
</tr>
<tr>
<td>Prefrontal lateral cortex</td>
<td>0.92</td>
<td>1.00 (0.89-1.11)</td>
<td></td>
</tr>
<tr>
<td>Whole prefrontal cortex</td>
<td>0.92</td>
<td>1.01 (0.86-1.15)</td>
<td></td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>0.10</td>
<td>0.12 (0.08-0.17)</td>
<td></td>
</tr>
<tr>
<td>Whole frontal cortex</td>
<td>0.94</td>
<td>1.02 (0.88-1.14)</td>
<td></td>
</tr>
<tr>
<td>Whole temporal cortex</td>
<td>0.88**</td>
<td>0.96 (0.89-1.01)</td>
<td></td>
</tr>
<tr>
<td>Whole parietal cortex</td>
<td>1.01</td>
<td>1.04 (0.97-1.11)</td>
<td></td>
</tr>
<tr>
<td>Whole occipital cortex</td>
<td>1.18***</td>
<td>1.00 (0.87-1.12)</td>
<td></td>
</tr>
<tr>
<td>Limbic cortex</td>
<td>0.85</td>
<td>0.87 (0.74-0.99)</td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>1.05</td>
<td>1.06 (0.91-1.22)</td>
<td></td>
</tr>
<tr>
<td>Lentiform nucleus</td>
<td>1.05</td>
<td>1.08 (0.82-1.34)</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>1.00</td>
<td>1.09 (0.86-1.31)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.17</td>
<td>0.94 (0.70-1.16)</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001 vs normal controls.
† Includes the thalamo-prefrontal lateral cortices.
‡ Includes the prefrontal and the precingulate cortices.
§ Includes the caudate and lentiform nuclei.
supranuclear palsy, which also affects this loop and in which an abnormal anteroposterior metabolic gradient has also been documented. On the other hand, lesions essentially confined to the substantia nigra, as in Parkinson's disease, do not consistently alter cortical metabolism. It is tempting to envisage dysfunction in the prefronto-striato-pallido-thalamo-prefrontal loop as one possible mechanism underlying both "athymorhnia" 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 schizophrenia or other anteroposterior degenerative disorders, where a flat affect and loss of drive are common features.

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

Addendum

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

We express our gratitude to the cytologist and radiochemistry staff of Ciceron for preparing "FDG, and to Ms Ravenel (Cytogen) for performing the statistical analysis.

L. Leveque, P. Lebailly, C. Polo, and N. Deramecourt

Correspondence to: J-C Baron, Inserm U 320, Ciceron, BP 5027, 14021 Caen cedex, France.


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. Other studies on this subject have used volumetric estimations of the hippocampal complex or temporal lobe. Thus 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 controls), of whom demographic data and MRI had been described elsewhere. The volumetric assessments were carried out by one author, who had been involved in the clinical part of the previous study and 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 digitized 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 grayscale 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 division, 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".

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 in an early Alzheimer's disease, if we 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. For clinical practice, however, visual ratings provide a useful and rapid assessment of hippocampal atrophy that correlates well with linear and volumetric measurements and may be used to aid the clinician in diagnosing or ruling out Alzheimer's disease.

P VERMERSCHE
D LEYS
Department of Neurology, Hôpital B, University of Lille, 59037 Lille Cedex, France

P SCHELTENS
Department of Neurology
F BARKHOF
Department of Diagnostic Radiology, Free University Hospital, PO Box 7057, 1007 MB Amsterdam, The Netherlands

Correspondence to: Dr P Scheltens, Department of Neurology, Free University Hospital, PO Box 7057, 1007 MB Amsterdam, The Netherlands.

Serum concentrations of 2',3'-dideoxyadenosine 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. Furthermore, it is associated with physical symptoms, such as muscle soreness, sore throat, arthralgia, myalgia, as well as psychological symptoms such as headache, insomnia, depressive state, and neuropsychiatric symptoms. It has often been claimed that the onset of chronic fatigue syndrome follows an upper respiratory tract infection or infection-like illness; hence a certain microorganism(s) or virus may cause it. Another possible candidate for inducing chronic fatigue syndrome is an activated cellular or humoral immune dysfunction, which has
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