Parkinson’s disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography

Thomas Becker, Georg Becker, Jochen Seufert, Erich Hofmann, Klaus W Lange, Markus Naumann, Alfred Lindner, Heinz Reichmann, Peter Riederer, Helmut Beckmann, Karlheinz Reiners

Abstract

Objectives—Depression is a frequent symptom in Parkinson’s disease. Compelling evidence suggests a role of the brainstem in the control of mood and cognition. In patients with unipolar depression transcranial sonography (TS) studies have shown structural alteration of the mesencephalic brainstem raphe which could suggest an involvement of the basal limbic system in the pathogenesis of primary mood disorders. The objective of the present study was to evaluate whether a similar alteration could be found in depressed patients with Parkinson’s disease using TS.

Methods—Thirty patients with Parkinson’s disease and 30 age and sex adjusted controls were examined by TS. Raphe echogenicity was rated semiquantitatively. The severity of motor symptoms and depression was rated using standard research instruments.

Results—Raphe echogenicity was significantly reduced in depressed patients with Parkinson’s disease compared with non-depressed patients with Parkinson’s disease and control subjects. Raphe echogenicity correlated negatively with degree of motor impairment, and differences in raphe echo between depressed and non-depressed patients with Parkinson’s disease were upheld when motor impairment was controlled for.

Conclusion—These preliminary findings suggest that, as in unipolar depression, a morphological alteration of the brainstem raphe might be involved in the pathogenesis of depression in Parkinson’s disease. This raphe alteration may reflect involvement in the basal limbic system in the pathogenesis of secondary depression. This concept is in line with current knowledge on the pathogenesis of both depression in Parkinson’s disease and primary depressive disorders.

Keywords: Parkinson’s disease; depression; basal limbic system; transcranial sonography

Depression and anxiety have commonly been recognised in patients with Parkinson’s disease. The average prevalence of depression in Parkinson’s disease is around 40% with a range from 4%-70%. Although it is evident that the degree of impairment and psychological and social factors influence the mood of patients with Parkinson’s disease, there are several lines of evidence pointing towards organic factors in the pathogenesis of depression in the disease. Transcranial sonography (TS) is a valuable tool in visualising both normal and diseased brain parenchyma, and brainstem anatomy can be reliably depicted. In a TS study in patients with Parkinson’s disease the substantia nigra was found to be hyperchogenic, which is thought to reflect tissue degeneration.

Recent TS studies provide evidence of structural alteration in the brainstem in patients with major depression. In two studies of a total of 140 psychiatric patients and 60 controls we assessed the echogenicity of the mesencephalic brainstem raphe and found a significant reduction of raphe echogenicity in unipolar depressed patients (not in bipolar disorder or schizophrenia). The raphe echo identified in the midline of the pontine and mesencephalic brainstem corresponds to fibre tracts and nuclei associated with the diencephalic limbic system (basal limbic system). Therefore, findings point towards a morphological alteration of the basal limbic system as one potential pathogenetic factor in depression.

In the present TS study we assessed raphe echogenicity in patients with Parkinson’s disease with and without concomitant depressive syndromes to examine whether alteration of the raphe system could be a common denominator in the pathogenesis of depressive syndromes.

Patients and methods

PATIENTS

Thirty patients with Parkinson’s disease (mean age 68.3 years; five women, 25 men) were included. They had all been outpatients at the Department of Neurology for more than one year and fulfilled research criteria for probable Parkinson’s disease. One neurologist (HR) in charge of the department’s specialist Parkinson’s disease outpatient clinic who was not involved in subsequent clinical or sonographic examinations selected patients with Parkinson’s disease both with and without depressive
symptoms. The aim was to include about equal numbers of patients with Parkinson’s disease with and without depression. Two patients with Parkinson’s disease (67 and 72 year old women, Hoehn and Yahr grades 2 and 3), in a total sample of 32 patients with Parkinson’s disease who underwent TS, were not included in this study because they had no sufficient acoustic bone window for transcranial sonography. The echogenicity of the substantia nigra and the width of the ventricular system in the same group of patients with Parkinson’s disease (n=30) have been reported elsewhere.74

All patients with Parkinson’s disease received optimised medical treatment, including anti-Parkinson’s disease medication (average doses of medication and numbers of patients using that medication were levodopa 510 mg/day (n=20), carbidopa 481 mg/day (n=9), lisuride 0.6 mg/day (n=5), bromocriptine 9.8 mg/day (n=10), amantadine 283 mg/day (n=3), selegiline-HCL 8.3 mg/day (n=12)). All patients received physiotherapy. In addition, six patients were taking antidepressant medication (average amitriptyline dosage 50 mg/day (n=4), doxepin 20 mg/day (n=4)). Duration of Parkinson’s disease ranged from 1 to 20 years (mean duration 9.7 (SD 5.8) years). All patients gave informed consent according to the Declaration of Helsinki.

RESEARCH INSTRUMENTS

All 30 patients with Parkinson’s disease first underwent TS, and subsequently had neurological and psychiatric examinations performed by another physician, all on the same day. Hoehn and Yahr grades of patients with Parkinson’s disease ranged from stages 2 to 4.30 The severity of Parkinson’s disease was quantified using the Columbia University Rating Scale (CURS).31 At the time of TS examination, mean score (SD) on the CURS rating scale was 27.7 (13.1). The psychiatric evaluations were performed using a semistructured psychiatric interview. The psychiatric diagnosis was made according to the diagnostic criteria of DSM-III-R.32 Patients were diagnosed as depressed only if the descriptive criteria of a major depressive syndrome (criterion A, diagnostic criteria for major depressive episode33) were fulfilled. The severity of depressive symptoms was assessed using the 21 item Hamilton depression scale (HDS). The mini mental state examination (MMSE) was administered to rule out dementia syndromes.33 The overall severity of depression was assessed using the clinical global impression (CGI) score.35 Following a suggestion by Starkstein et al14 HDS items on early morning awakening, anergia, and motor retardation (items 5-8, 13, and 16) were excluded in an additional analysis because ratings on these items did not differ between depressed and non-depressed patients with Parkinson’s disease. This reduced HDS is designated HDS*. All patients were asked to complete the “Befindlichkeitsskala” by von Zerssen (Bf-S).33

CONTROL GROUP

As a comparison group, 30 age and sex adjusted control subjects without Parkinson’s disease (mean age 65.2 years, six women, 24 men) underwent neurological, psychiatric, and TS examinations, and the questionnaires listed above were completed. Neurological diagnoses of controls were as follows: seven patients had a cerebral ischaemia (time since the first ischaemic event ranged from one to 18 months with a median of six months), seven patients had been referred due to disc herniation (with a history of back pain of up to 11 years), three had supratentorial brain tumours, and two had myelopathy. Two patients had myasthenia gravis, two had a diagnosis of peripheral neuropathy, one epilepsy, and one patient had a subarachnoid haemorrhage. In addition, five healthy subjects were included. None of the control subjects had parkinsonian symptoms or symptoms fulfilling DSM-III-R criteria of depression.

TRANSCRANIAL SONOGRAPHY

For TS examination we employed a colour coded, phased array ultrasound system, equipped with a 2.25 MHz transducer (Sonoline CF, Siemens, Erlangen, FRG). The axial resolution of the method in the focus zone is about 1 mm. Results of the TS examination depend on the examiner’s skill, and all TS examinations were carried out by one experienced examiner (GB) who was unaware of the psychiatric status of the patient. Patients were asked to lie on the examination table in a supine position while TS was performed through a preauricular acoustic bone window. The ultrasound system indices chosen were: penetration depth 16 cm, dynamic range 45 dB, high persistence, reject 7; image brightness and time gain compensation were adapted to the requirements of the special examination situation. Supratentorial and infratentorial brain areas were scanned in axial planes by tilting the probe at the acoustic window.

The mesencephalic brainstem can be depicted as a butterfly shaped structure of low echogenicity surrounded by the hyperechogenic basal cisterns (figure). The red nuclei, the aqueduct, and the brainstem raphe are hyperechogenic areas within the mesencephalon.17 25 26 The aim of the TS examination was to identify the pontine and mesencephalic brainstem raphe (ascending and descending pathways and brainstem nuclei adjacent to midline). The picture showing the best raphe visualisation was selected for analysis. Echogenicity of the brainstem raphe was rated semiquantitatively on a three point scale using the hyperechogenic red nucleus as a reference point: 1=raphe not visible/ isoechogenic raphe compared with adjacent brainstem parenchyma, 2=slightly echogenic raphe, 3=normal raphe echogenicity (echogenicity of the raphe is identical to that of the red nucleus). For technical reasons further quantification of ultrasound echogenicity is not feasible.37 Printouts of TS images were re-evaluated by a second, independent ultrasound examiner (MN) to assess interrater reliability. Also, the width of the third ventricle was
determined by measuring the maximal transverse diameter in the axial scanning plane. Frontal horn size was assessed by measuring the maximal distance between the origin of the septum pellucidum and the tip of the frontal horn.

STATISTICAL ANALYSIS

Interrater reliability of raphe ratings was calculated by rank correlation and weighted variance (kw) (previous work having shown that satisfactory agreement is reached when TS is performed by two different examiners). The statistical plan included three sequential two-group comparisons of (1) depressed versus non-depressed patients with Parkinson’s disease, and (2) and (3) of each of the patient groups versus the control group. Between group comparisons were performed using the $\chi^2$ test. The correlations of different indices (scores on clinical rating scales, raphe echogenicity) were performed using Spearman’s rank correlation. The influence of clinical ratings which might confound group differences was examined using analysis of covariance (ANCOVA). Group differences for continuous variables (for example, ventricular width) were examined using the Mann-Whitney U test.

Results

CLINICAL DATA

Thirteen of the 30 patients with Parkinson’s disease fulfilled the diagnostic criteria of a major depressive syndrome according to DSM-III-R (mean age 67.7 years; two women, 11 men), 17 patients with Parkinson’s disease were not depressed (mean age 68.5 years; two women, 15 men). Three of the 13 depressed patients with Parkinson’s disease had mild depression, four had moderate depression, and six had severe depression. Psychomotor retardation was reported in 12 of the 13 depressed patients with Parkinson’s disease, insomnia, and early morning awaking in 10, loss of appetite in eight, somatisation in seven, past or present suicidal ideation in seven, and delusions in five. The duration of the depressive symptoms ranged from three to 13 years (mean duration 7.6 (SD 4.2) years) and in two patients depression predated the manifestation of motor impairment. The differences in MMSE were only slight and failed to reach significance (Mann-Whitney U test, $P=0.49$; table 1).

Motor disability was found to be more severe in depressed (CURS: 33.4) than in non-depressed (CURS: 23.4) patients with Parkinson’s disease (this difference failed to reach significance: Mann-Whitney U test, $P=0.051$; table 1).

RAPHE ECHOCENTICITY

The level of agreement on raphe echogenicity between the two raters was high (in 15 out of 30 cases assessments differed by one score on the rating scale, there was no instance of a two point score difference; rank correlation: $r=0.81$, $P<0.001$, concordance analysis: $kw = 0.74$, variance ($kw = 0.01$, $P<0.0001$).

In the group of patients with Parkinson’s disease with depression raphe echogenicity was distinctly reduced compared with non-depressed patients with Parkinson’s disease and controls; the distribution of raphe echogenicity scores in controls was very similar to that found in non-depressed patients with Parkinson’s disease (table 2). The figure shows two examples of TS images. Differences in raphe echogenicity between depressed and non-depressed patients with Parkinson’s disease and between depressed patients with Parkinson’s disease and controls were significant ($\chi^2$: both $P<0.01$). There was no significant difference between echogenicity scores in non-depressed patients with Parkinson’s disease and controls ($\chi^2$: $P=0.72$).

CLINICAL CORRELATIONS

Correlations of demographic data and severity of illness with raphe echogenicity were examined. No correlation was found between raphe echogenicity and age (Spearman’s rank correlation, $\rho=-0.101$, $P=0.597$). Mean echogenicity scores in women and men were similar (women: 2.6 (SD 0.6), men: 2.8 (SD 0.5), $\chi^2$, $P=0.09$). By contrast, raphe echogenicity in patients with Parkinson’s disease was significantly correlated with the overall severity of depression as assessed by CGI ($\rho=-0.646$, $P<0.001$), with HDS ratings (HDS: $\rho=-0.594$, $P<0.001$; HDS*: $\rho=-0.57$, $P=0.001$), with self assessment of depressive symptoms (Bf-S: $\rho=-0.489$, $P<0.05$), and with motor impairment as assessed by CURS (Spearman’s rank correlation, $\rho=-0.38$, $P=0.03$). However, the association between reduced raphe echogenicity and depressive state remained significant when the CURS score was included as covariate in an ANCOVA analysis ($F_{1,1}=7.1$, $P<0.01$).

When motor disability (CURS) was related to the severity of depressive symptoms as

<table>
<thead>
<tr>
<th>Scale</th>
<th>Depressed PD patients (n=13) mean (SD)</th>
<th>Non-depressed PD patients (n=17) mean (SD)</th>
<th>Control subjects (n=30) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURS</td>
<td>33.4 (11.8)</td>
<td>23.4 (12.7)</td>
<td>1.6 (2.1)</td>
</tr>
<tr>
<td>CGI</td>
<td>5.3 (1.1)</td>
<td>2.1 (0.3)</td>
<td>2.0 (—)</td>
</tr>
<tr>
<td>HDS</td>
<td>24.3 (7.9)</td>
<td>2.5 (3.6)</td>
<td>1.6 (1.9)</td>
</tr>
<tr>
<td>HDS*</td>
<td>14.2 (6.2)</td>
<td>1.1 (2.0)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Br-S</td>
<td>39.5 (12.2)</td>
<td>9.5 (9.9)</td>
<td>5.5 (5.5)</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.2 (3.2)</td>
<td>27.1 (2.7)</td>
<td>28.6 (1.5)</td>
</tr>
<tr>
<td>Width of 3rd ventricle (cm)</td>
<td>0.9 (0.3)</td>
<td>0.8 (0.3)</td>
<td>0.7 (0.2)</td>
</tr>
<tr>
<td>Width of frontal horn (cm)</td>
<td>2.1 (0.2)</td>
<td>1.8 (0.3)</td>
<td>1.7 (0.3)</td>
</tr>
</tbody>
</table>

HDS*=HDS item counts excluding HDS items 5, 6, 7, 8, 13, 16 which assess early morning awakening, anergia, and motor retardation.

Table 2  Raphe echogenicity scores in depressed patients with Parkinson’s disease (PD), non-depressed patients with PD, and controls

<table>
<thead>
<tr>
<th>Raphe echogenicity scores</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed PD patients (n)</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Non-depressed PD patients (n)</td>
<td>1</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Control subjects (n)</td>
<td>1</td>
<td>12</td>
<td>17</td>
</tr>
</tbody>
</table>
TS brainstem images and schematic illustrations in (A,B) non-depressed and (C,D) depressed patients with Parkinson’s disease (axial scanning plane through the mesencephalic brainstem). In both patients the mesencephalic brainstem is illustrated as a butterfly shaped area of low echogenicity surrounded by the hyperechogenic basal cisterns. (A) In the non-depressed patient with Parkinson’s disease the brainstem raphe (arrow) is unequivocally visualised as a hyperechogenic midline structure in contact with the aqueduct (arrowhead). (C) It is not identified in the depressed patient with Parkinson’s disease. In both patients with Parkinson’s disease the substantia nigra exhibits increased echogenicity, probably due to iron inclusion or microgliosis (small arrows)."  
1 = mesencephalic brainstem; 2 = hyperechogenic basal cisterns; 3 = choroid plexus."
assessed by HDS and HDS* significant relations were disclosed (HDS: $\rho=0.3$, $P<0.05$; HDS*: $\rho=0.5$, $P<0.05$). However, no correlation was found between raphe echogenicity and substantia nigra echogenicity ($\rho=-0.17$, $P=0.35$). Comparing measures of ventricular width in subgroups of patients with Parkinson’s disease, a significant enlargement of the lateral ventricles was found in depressed patients with Parkinson’s disease compared with non-depressed patients (Mann-Whitney $U$ test, $P<0.05$), whereas differences in width of the third ventricle failed to reach significance (Mann-Whitney $U$ test, $P=0.5$).

Discussion
In the present study we found a significant reduction of mesencephalic brainstem raphe echogenicity in patients with Parkinson’s disease with depression compared with non-depressed patients with Parkinson’s disease and non-depressed, non-parkinsonian controls. These findings resemble the decrease in raphe echogenicity previously reported in primary unipolar depression.25 26 Lateral ventricular enlargement was also found, and this is in line with previous CT and MRI studies in old age depression and in depressed patients with Parkinson’s disease.27 28

LIMITATIONS OF THE STUDY
Patients with Parkinson’s disease were not recruited from an epidemiologically representative sample but from the selected patient group of a tertiary referral centre. In the control group (of 30), 18 subjects were either healthy probands or patients with non-cerebral neurological disorders, whereas cerebral ischemia was the largest diagnostic group ($n=7$) among the remaining 12. In this group an impact of the CNS disorder on raphe echogenicity could not be ruled out. However, the distribution of raphe echogenicity scores in the control group was closely similar to findings in healthy adults reported previously.25 26 Also, the design of the study included three way group comparisons (depressed Parkinson’s disease, non-depressed Parkinson’s disease, controls) in which the above reservation did not apply to the comparison between the first two groups.

Methodological restraints of TS may raise further concerns. Whether a structure is depictable or not depends, in part, on the insonation angle. Therefore, TS is dependent on the examiner’s skill, and standardisation of TS examination is limited by variables such as the acoustic bone window and angulation of the scanning plane. Echogenicity assessment requires a semiquantitative assessment (a rater judgement), and the TS examiner in the present study (who was also one of the two raters) met patients when he performed TS. Thus blindness to diagnosis might be questioned. This does not primarily refer to the rating process (good reliability being achieved with another rater not present at the time of TS examination). The problem lies in a potential impact of clinical bias on the TS examination itself. On the other hand, hypokinesia and anamia were features in virtually all patients with Parkinson’s disease examined in this study (of whom only 43% were depressed). Thus gait and facial expression could not be considered sufficient clues to the mood status of patients, and the examiner did not enter into conversation before the end of TS examination and echogenicity rating. Blindness to the psychiatric status was, therefore, achieved to the best of our means. However, replication of the present findings is mandatory, and further confirmation through MRI or pathological studies is required.

BASAL LIMBIC SYSTEM INVOLVEMENT
The present results in patients with a secondary form of depression corroborate the hypothesis that morphological alteration of the mesencephalic raphe is involved in the pathogenesis of depressive disorders in general. Changes in raphe echogenicity reflect changes in tissue impedance and point towards an alteration of the brainstem microarchitecture which could be due to a shift in tissue cell density, a change in interstitial matrix composition, or an alteration of fibre tract integrity. Sonographically, the brainstem raphe presents as a homogeneous area. However, anatomically, it corresponds to a network of mesencephalic nuclei and fibre tracts that are part of the basal limbic system.27 28 37 38 These fibre tracts bidirectionally link nuclei of the pontine and mesencephalic midline region with diencephalic and telencephalic brain areas. They unite dopaminergic fibre tracts originating mainly from the ventral tegmental area, serotonergic projections from the superior central nucleus and the dorsal raphe nucleus, and noradrenergic fibres from the locus coeruleus within the territory of the mesencephalic raphe.39 40

Various anatomical, physiological, and biochemical findings underline the importance of the basal limbic system for affective equilibrium, and compelling evidence suggests that the nuclei, fibre tracts, and neurotransmitter systems associated with the basal limbic system are involved in the pathogenesis of primary depression and depression in Parkinson’s disease41–43. (1) Histopathological studies have documented a pronounced reduction of cell density in the brainstem nuclei of the basal limbic system such as the ventral tegmental area, locus coeruleus, and dorsal raphe nucleus in patients with Parkinson’s disease and patients with Alzheimer’s disease with depression.44–46 (2) PET studies suggest hypometabolism in the medial frontal cortex, a major projection area of the basal limbic system, in patients with Parkinson’s disease and concomitant depression resembling findings in primary depression.47–49 (3) Several studies have shown low concentrations of dopamine, serotonin, and noradrenaline or their metabolites in the CSF of depressed patients with Parkinson’s disease50–54. (4) In animal studies, lesions of the raphe nucleus, peduncular grey, or locus coeruleus and their projections elicit some of the symptoms found in depressive illness.55–59
IMPLICATIONS

Evidence from TS studies in primary and secondary depression suggests a pathogenetic role of an alteration of ascending and descending neuronal pathways in the brainstem or mesencephalic brainstem nuclei with a concomitantly altered pattern of neurotransmission. The similarity of sonographic, PET, and neurochemical findings in unipolar depression and Parkinson's disease indicate that alteration in the basal limbic system may be a typical "pathway" in the pathogenesis of depressive illness.

We thank Andreas Jager for statistical support.


Paul Ferdinand Gachet (1828–1909)

Paul Ferdinand Gachet was a general practitioner with a training in medical ailments. His thesis (1858) entitled *Étude sur la Mélancholie* contained principles for the moral treatment of the insane. Gachet’s system of therapy for melancholies was based on three principles, admission to hospital, therapeutic activities, and psychological support. For physical therapy Gachet allowed the use of warm baths to calm anxious patients. He strongly condemned the prevalent use of phlebotomy and purgation.

Gachet looked after Van Gogh during the painter’s last two months of life in Auvers-sur-Oise in 1880. He was an early supporter of the impressionists and a painter and engraver of considerable talents himself. He was intrigued by the creative mind. His campaign for the establishment of a Society for Mutual Autopsy in which artists would leave their brains for postmortem study to evaluate artistic ability and elucidate the process for creativity met with little enthusiasm. Renoir was one who resisted that invitation. Paul Gachet’s medical records pertaining to Van Gogh have not been found. Gachet had spoken with Theo Van Gogh before seeing Vincent. Theo, in a letter to Vincent, relayed the news that “When I told him how your crisis came about he said to me that he didn’t believe it had anything to do with madness and that if it was what he thought he could guarantee your recovery, but that it was necessary to see you and to speak with you in order to make a more definitive statement”.

There is anecdotal evidence that Gachet considered that Van Gogh had been overexposed to turpentine vapour, and that painting for long hours in the sun contributed to his illness. There are many views on the nature of Van Gogh’s illness. Gachet seems to have considered it as more akin to epilepsy without convulsions complicated by periods of depression. He was not convinced that Vincent had pure insanity. Two months after becoming a patient of Dr Gachet, in the late Sunday afternoon of 27 July 1890, Van Gogh shot himself in the chest with a revolver. Dr Gachet found that the bullet had been deflected by the fifth rib. He died on 28 July about 130 am. Gachet persuaded the village priest to make an exception and allow this victim of suicide to be buried in the cemetery, not far from the artist’s “vast fields of wheat”. Dr Gachet had firm views about psychiatric illness. In a letter to the editor of *Le Figaro* (18 August 1859) Gachet condemned a previous article claiming mental illness to be contagious pointing out the obvious that if this was true, an epidemic of insanity should have occurred years earlier among the employees of the Salpetiere. In 1875 through the pages of a popular health annual read by a large audience, Dr Gachet proclaimed, contrary to widely held opinion, that insanity was curable. He attacked the law of 1838 which allowed almost unregulated confinement of the mentally ill and concluded by suggesting that the public should divest themselves of the idea that mental illness “is an exaggeration or a deviation of intelligence and that people who are taxed with originality are monomaniacs and are insane”.

In 1990 Antigua published a set of stamps to commemorate the centenary of the death of Vincent van Gogh. Among these is Van Gogh’s portrait of Dr Gachet (Stanley Gibbons 1517, Scott 1426) painted in two days in June 1880. The painting hangs in the Musee D’Orsay in Paris.

LF HAAS

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