

Walking difficulties in patients with Alzheimer's disease might originate from gait apraxia

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Objectives: To investigate whether gait apraxia is a possible cause for some of the walking abnormalities shown by patients with Alzheimer's disease.

Methods: 60 patients with Alzheimer's disease, selected as being free from overt extrapyramidal impairment or other potential causes of walking deficits, were assessed with a new test evaluating aspects of walking and related movements. Norms for this test were collected from a sample of 182 healthy volunteers.

Results: 40% of the Alzheimer group performed below the cut off score on this test, and half performed poorly. Performance of the Alzheimer group in the walking skills test correlated highly with scores in a test assessing limb apraxia and with dementia severity.

Conclusions: Gait apraxia may be the cause of walking disorders found in a subgroup of patients with Alzheimer's disease. Its detection is made easier by the use of a standardised test, but still relies heavily on the exclusion of other causes of walking deficits. It is a recognisable and independent form of apraxia.

Some patients with Alzheimer's disease have walking difficulties.¹ When these difficulties occur, patients walk with slow and irregular steps and find it hard to negotiate turns, climb onto a stepping stool, avoid obstacles in their path, or lie down and rise from the doctor's couch.^{2–4} A study showed that about three years after diagnosis, 50% of Alzheimer patients reported problems in walking, and of these 33% were classified as non-ambulatory.³ These clinical observations have been confirmed by experiments that showed that patients with Alzheimer's disease walk more slowly than healthy elderly people.^{5–6} These walking problems are acknowledged in most reviews of motor deficits in Alzheimer's disease⁷ and are interpreted as manifestations of the extrapyramidal deficits which affect 12–28% of Alzheimer patients, or as side effects of drug treatment—for example, with neuroleptic agents.^{8–9} However, Alzheimer patients without apparent extrapyramidal signs may also show overt problems in walking and trunk movements. Kurlan *et al*¹⁰ maintain that a proportion of these individuals may be affected by "frontal gait disorder,"¹¹ a syndrome coterminous with gait apraxia. A similar view was championed by Visser.¹²

Meyer and Barron¹³ defined gait apraxia as "the loss of ability to properly use the lower limbs in the act of walking." Gait apraxia^{11–16} includes disturbances of trunk movements, standing, and walking (*Rumpf, Stand und Gangapraxie*,¹⁷) that are not caused by orthopaedic abnormalities (for example, bone and joint degeneration), muscle wasting, arteriosclerosis obliterans of the lower limbs, pyramidal deficits, ataxia (cerebellar, vestibular or proprioceptive), dystonias and dyskinesias (from diseases that involve the basal ganglia), psychiatric disease (for example, schizophrenic mannerisms¹⁸), side effects of drugs,¹⁹ or "cautious gait" because of fear of falling (also known as "trepidante Abasie"^{20–21} or stasobasophobia^{22–23}).

Several forms of apraxia have been reported in patients with Alzheimer's disease,^{24–27} though walking problems and trunk movement deficits have been underinvestigated in this condition.¹⁰

Our aim in the present study was to verify whether such patients show any walking disorders that cannot be accounted for by the causes listed above. These disorders

would be interpreted as resulting from gait apraxia. A secondary aim was to investigate the relation between gait apraxia and limb apraxia.

METHODS

Participants

Participants were selected from among patients with Alzheimer's disease who did not present with any concomitant known disorder that could affect their walking. Six degenerative diseases were targeted for exclusion, using formal diagnostic criteria: dementia with Lewy bodies,²⁸ idiopathic Parkinson's disease,²⁹ progressive supranuclear palsy,³⁰ corticobasal degeneration,³¹ frontotemporal dementia,³² and vascular dementia.³³

The patients considered for the study were drawn from a consecutive series of 89 patients referred to the dementia neuropsychology unit of the neurology department, University of Milan, San Paolo Hospital, with a diagnosis of progressive cognitive deterioration from possible or probable Alzheimer's disease (NINCDS-ADRDA criteria³⁴). Twenty four of these were excluded: five were unwilling to participate or were affected by disabling degenerative disease of the hip or knee joints; 11 had extrapyramidal signs (for example, resting tremor, rigidity) severe enough to suggest a concomitant extrapyramidal disease; and eight had hallucinations or were under treatment with neuroleptic drugs. The two step exclusion procedure (exclusion of patients with other dementias and with concomitant disorders) considerably lowered the likelihood that the patients included in our sample were affected by extrapyramidal symptoms or non-Alzheimer dementias.

The final study cohort comprised 65 outpatients (16 men, 49 women). Three of these were subsequently excluded from analysis because it became apparent during debriefing that they had a poor understanding or recollection of the task instructions. Two further patients were excluded because

Abbreviations: AWS, assessment of walking skills; MODA, Milan overall dementia assessment

Table 1 Demographical features and dementia severity of (A) the 60 patients with Alzheimer's disease included in this study, and (B) the nine patients who formed a subgroup with walking difficulties at the initial clinical examination

	Mean (SD)	Observed range
(A) Alzheimer's disease group (n = 60)		
Age (years)	72.5 (8.7)	51 to 88
Education (years)	7.1 (4.0)	3 to 19
MODA (scale range 0–100; cut off 85.5)	67.2 (14.4)	31.2 to 87.7
(B) Subgroup with walking difficulty (n = 9)		
Age (years)	65.9 (8.5)	51 to 78
Education (years)	7.8 (4.3)	3 to 19
MODA (scale range 0–100; cut off 85.5)	52.6 (19.2)	31.2 to 87.7

MODA, Milan overall dementia assessment.

they did not complete the test, leaving a final study population of 60 patients. Twenty one (35%) of these 60 patients entering the final analyses were less than 70 years old. All had a structural brain scan with either computed tomography (CT) (46 cases) or magnetic resonance imaging (MRI) (14 cases); these had been carried out to exclude the presence of tumour or large vascular lesions. Small vascular lacunae were detected by CT in two patients and by MRI in five others; these seven patients were included in the study as their clinical history and disease progression were strongly suggestive of Alzheimer's disease.³⁵

The severity of cognitive deterioration was evaluated by a neuropsychologically oriented psychometric severity scale (the Milan overall dementia assessment (MODA)³⁶), the score of which ranges from 0 (worst score) to 100 (cut off score = 85.5/100, which corresponds to the outer tolerance limit in the normal population). Raw MODA scores are adjusted to account for the effect of age and education. This dementia assessment tool correlates highly ($r = 0.87$) with the mini-mental state examination^{36, 37} and was chosen because it offers more extensive testing of cognitive abilities.

Demographic and clinical features of the sample are summarised in table 1A; the median for the MODA was 70.5. From the clinical notes taken at the time of the first examination, it appears that gait problems (or problems in rising from a chair or turning in bed) were prominent in nine of the 60 patients (15%) included in the study (one of these had neuroradiological signs of white matter changes). The demographic features of this subgroup of nine patients are given in table 1B.

Assessment of walking skills

A new test was devised to assess walking and related movements. In the selection of the items composing this test, the multiple features characterising gait apraxia^{11, 38} were considered. Zingerle³⁹ categorised these into four groups:

- inappropriate righting and supporting reactions when going from lying and sitting to the upright position;
- disequilibrium while walking;
- unnecessary and superfluous (literally "parasitic"⁴⁰) or dyskinetic movements;
- locomotor disorders including gait initiation failure,^{14, 41} irregularities of rhythm, size, speed, and direction of steps, uncoordinated movements of trunk, lower limbs, and upper arm swinging, and inability to negotiate turns.

In summary, gait apraxia causes clumsy and bizarre trunk and leg movements, leading to ineffective propulsion. Hence, both the gait itself and the trunk movements were considered

in the assessment of walking skills. As with all tests assessing apraxia, this instrument is not diagnostic either for the underlying disease or for gait apraxia. Once all other potential causes of impairment of walking have been excluded, performance on the assessment of walking skills is taken as a measure of gait apraxia.

Characteristics of the assessment of walking skills

The assessment of walking skills (AWS) included 42 items (plus four items used as run-in examples) devised to assess trunk and gait, partly derived from earlier work^{13, 14, 38, 39, 41} and partly devised de novo. The items included in the final version of the test were selected through a series of pilot studies and were grouped into two components: assessment of trunk movements (22 items) and walking component proper (20 items). The total score for walking skills ranged from zero to a best of 42. Practice items were available for the two individual components of the test. A list of items for the two components of the assessment of walking skills is given in the appendix.

Assessment of administration and scoring procedures for the AWS

Instructions were standardised. Each item was demonstrated and verbally described by the examiner. The participants had to respond by imitation immediately after presentation. This procedure was employed in order to minimise potential confusion between apraxic and verbal comprehension errors. Two examiners were present, one demonstrating the items and the other observing, interacting, and recording the patient's performance. Participants were debriefed at the end of the session so as to reassure the examiner that they had understood and remembered the rules of the task. Administration time was approximately 40 minutes. An item was scored as pass or fail according to a set of rules derived from previous studies of apraxia.⁴² An item was considered as failed when performance was clearly inaccurate, such as crossing the legs while attempting to walk,¹⁴ or when the performance was hampered by the inability to keep an upright stance,⁴⁰ accompanied by parasitic arm and trunk movements or bizarre leg movements, or impeded by impaired balance (for example, "*déséquilibre frontale*"—frontal imbalance⁴³). Items were also considered as failed when the general organisation of the movements was relatively preserved but their execution lacked dexterity (for example, "*eigentliche Ungeschicklichkeit*"⁴⁴—overwhelming lack of dexterity; "*bewegunstechnische Schwierigkeit*"¹⁷—halting movement execution; "*Tapsigkeit*"⁴⁵ or "*Unbeholfenheit*"⁴⁶—awkwardness). An item generating no response after several solicitations was also scored as a fail.

Normative data were gathered from a sample of 182 healthy volunteers (123 women and 59 men; mean (SD) age 56 (21) years, range 20 to 92; 96 were Italian and 86 British).

Table 2 Mean performance on the assessment of walking skills achieved by the 182 healthy controls subdivided according to age decade

Age group (years)	n	AWS score (0–42)
20 to 29	36	41.9 (0.03)
30 to 39	5	42 (0)
40 to 49	17	42 (0)
50 to 59	38	41.9 (0.2)
60 to 69	26	41.8 (0.3)
70 to 79	28	40.9 (1.8)
80 to 92	32	38.2 (5.0)

AWS score values are mean (SD).
AWS, assessment of walking skills.

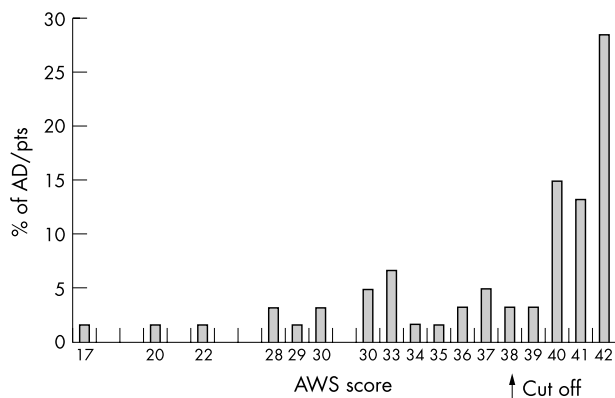


Figure 1 Distribution of patients with Alzheimer's disease according to the assessment of walking skills score.

Forty one of the controls entering the study (10 men, 31 women) were retested by a different examiner after five to seven days. As expected in a test assessing gait and related movements, the distribution of scores in healthy controls was pronouncedly skewed towards the top score (median 42; observed range, 30 to 42) and age was not relevant (table 2), although the variability increased in individuals older than 70 years. Inner and outer tolerance limits were computed by means of a non-parametric procedure.⁴⁷ The outer tolerance limit defines the score at which, or below which, the probability that an individual belongs to the normal population is less than 5%. The outer tolerance limit (that is, 38) was used as cut off score. The test–retest reliability was 0.98.

Upper limb apraxia assessment

For upper limb assessment, we used the upper limb apraxia test, a test assessing ideomotor apraxia devised by De Renzi *et al.*⁴⁸ This is a 24 item imitation test consisting of half meaningful and half meaningless movements, half requiring to hold a posture and half the execution of a motor sequence. The total score ranges from zero to a best of 72. Participants were tested with their dominant hand. Fifty eight of the participating Alzheimer patients were tested with this task.

RESULTS

The mean (SD) score of the Alzheimer patients in the AWS was 37.33 (5.86), range 17 to 42. Figure 1 shows the distribution of performances on the AWS score in these patients. Thirty six (60%) of the patients scored above cut off. The performance of the remaining 24 patients (40%) was scattered across the range of possible scores, with a large proportion of the patients (30%) performing just below cut off (two of whom had evidence of white matter changes), while the remainder performed poorly. All the nine patients presenting with clinical signs of walking difficulties performed well below cut off in the AWS, their scores being among the lowest observed in the Alzheimer group. Their average score (27.3) differed significantly from that of the other 51 patients entering the study (39.6) ($F_{1,58} = 118.724$, $p < 0.0001$).

Poor performance on the AWS by the Alzheimer group could not be attributed to the number of non-responses to certain items, as from 2520 possible responses (42 items by 60 participants), there was only a negligible proportion of non-responses (136, or 5.4%). Moreover, the distribution of correct responses shows that the Alzheimer patients failed most items evenly, indicating that their poor performance cannot be ascribed to a cluster of particularly difficult items. Only two items (items 21 and 28 in the Trunk component) were passed by all patients, and only one item (item 20 in the Walking component) was failed by more than 40% of the

Alzheimer group). A *t* test analysis was run to compare the two parts of the test. There was no statistical difference between the two sets of items ($t_{40} = -1.64$, $p = 0.10$).

The Spearman correlation coefficient between dementia severity measured by the MODA and the AWS score was 0.47 ($p < 0.0001$). Indeed, only six of 29 Alzheimer patients with mild dementia (MODA score above 70) performed below the cut off score (21%), compared with 16 of 31 (52%) of those with moderate to severe dementia.

To evaluate whether the nine patients reporting walking difficulties on clinical examination had these problems because of the severity of their dementia, a correlation analysis was run between their MODA scores and their AWS scores. No significant correlation was found ($r = 0.046$, $p = 0.89$).

Twenty two of the 58 Alzheimer patients tested with the upper limb apraxia test performed below cut off (38%); the correlation between the limb apraxia test and the measure of dementia severity was 0.39 ($p < 0.005$). The correlation between the AWS scores and performance in the upper limb apraxia test was significant, at 0.50 ($p < 0.0001$). No correlation between the AWS scores and the upper limb apraxia scores was observed in the subgroup of nine patients who reported walking difficulties during the clinical examination ($r = -0.30$, $p = 0.37$). A stepwise regression procedure on the AWS scores, with age, dementia severity, and limb apraxia scores entered as independent variables, showed that all three were significant independent predictors of walking performance ($r = 0.23$, 0.53, and 0.50, respectively; $p < 0.0001$ in all cases).

DISCUSSION

Gait disturbances are not uncommon in Alzheimer's disease and have been observed also in Alzheimer patients carefully selected to be exempt from extrapyramidal, ataxic, and parietic signs or clinically relevant musculoskeletal impairments.³ Patients with Alzheimer's disease are at increased risk of losing their balance^{3,12} and falling compared with matched controls.^{4,19,49} Various studies have reported very different figures for prevalence of gait abnormalities, ranging from 8.7%⁵⁰ to over 90%,⁵¹ because of different inclusion criteria and different assessment procedures.

The lack of a standardised instrument to assess gait has been implicated as a possible cause for the low frequency of reports.² In this paper, a new test assessing walking skills was devised and norms collected to calculate cut off scores with population based inferential values. A large group of patients with Alzheimer's disease was tested with this new instrument, and a sizeable proportion (40%) scored below cut off, showing some deficit in their walking skills; a smaller proportion was severely impaired. These figures contrast with the 15% detected by simple clinical observation. Indeed the use of a standardised instrument has been openly advocated.⁵² Although the possibility of right–left confusion, working memory deficits, and problems with verbal comprehension was minimised by demonstrating the items, the complexity of some of them might have contributed to inflating the proportion of patients performing poorly. It is important to note, however, that items were scored as failed only when clear apraxic errors were observed.

The assessment of walking skills on its own cannot discriminate between walking disorders caused by gait apraxia and other neurological causes of walking difficulty. Thus to advocate the presence of gait apraxia, alternative causes of walking abnormalities in Alzheimer's disease have to be excluded for a start. The Alzheimer patients enrolled in this study had no overt extrapyramidal impairments or other concurrent neurological diseases. The presence of associated vascular pathology in a few patients also cannot account for the outcome. Neuroradiological signs of white matter

Table 3 Published reports of cases of gait apraxia in patients with degenerative and progressive paralysis caused by cerebral diseases

Author, year	Case	Age (years)	Sex	Localisation
Bonfiglio, 1908 ⁶³	LS	60	M	Brain atrophy (neurosyphilis, endoarteritis of Heubner artery)
Gerstmann & Schilder, 1926 ¹⁴	JM	41	M	Dementia*
Kleist, 1934 ⁴⁶	ZG	67, nr	FM	Pick's disease, L>R, predominantly F1, F2, F3; brain atrophy, predominantly F bilateral
Lange, 1936 ⁶⁴	nr	nr	nr	Pick's disease, predominantly F, R>L
Meyer & Barron, 1960 ¹³	2	68	M	Neurosyphilis, F bilateral atrophy
Petrovici, 1968 ⁵⁶	AC	56	W	Pick's disease, L>R, predominantly F
Rataj & Korohoda, 1969 ⁶⁵	LP	49	M	Parkinson plus
Tyrell, 1994 ¹⁶	1	70	W	Dementia*, hypometabolism (PET) bilateral medial F1 + cingulum.
Rossor <i>et al</i> , 1999 ⁶¹	2	69	W	Alzheimer's disease + corticobasal dementia, hypometabolism (PET) bilateral medial F1 + cingulum.

*No necropsy report available.

F, frontal, F1, F2, F3: first, second, and third frontal gyri; L, left hemisphere; nr, not reported; R, right hemisphere.

changes were reported in only three of the 24 patients who scored below cut off in the assessment of walking skills. As there are no plausible alternative interpretations that might account for the walking deficits observed in this highly selected sample of Alzheimer patients, by exclusion they are interpreted as resulting from gait apraxia.

One third of the Alzheimer patients performed below cut off on the upper limb apraxia test. This percentage is remarkably similar to those reported in previous studies.^{24 26} The AWS scores correlate highly with the scores achieved in the ideomotor apraxia test. The high correlation between the two sets of scores—which is not removed when dementia severity is considered—indicates an association between the two functions. This opposes the argument that gait apraxia should not be considered a true form of apraxia because of dissociation from limb apraxia⁵³ (for a discussion on double dissociations, see Dunn and Kirsner⁵⁴). Generally, gait apraxia refers to deficits of a relatively unitary function with no reference to a theoretical model. However, some investigators have classed gait apraxia among the melokinetic apraxias^{55 56}—*gliedkinetische Apraxie*⁵⁷ or *innervatorische Apraxie*⁵⁸—owing to the lack of hemispheric dominance and the characteristic clumsiness. Gait apraxia does not belong to the realm of ideational deficits—that is, patients with gait apraxia know what walking entails. Within the dichotomy proposed by Benke⁵⁹ between a conceptual system of motor acts and a system controlling sensorimotor and spatiotemporal features of movement, gait apraxia would arise from impairment of the latter system. Gait apraxia, which affects the performance of highly routinised synergistic actions, should also be distinguished from ideomotor apraxia, which hampers individual movements and meaningless gestures. Alzheimer himself suggested a possible dissociation between the presence of upper limb apraxia and the absence of gait disturbances in his patient Auguste D.⁶⁰

Gait apraxia should be considered as a possible cause of walking difficulties when there are walking abnormalities that cannot otherwise be accounted for in patients with moderate Alzheimer's disease, or indeed other dementias.⁵² Walking disorders have previously been attributed to gait apraxia in a few single case reports of patients suffering from cortical degenerative diseases (table 3). Kurlan *et al*,¹⁰ in their review of gait disorders in Alzheimer's disease, attributed these deficits to gait apraxia. Gait apraxia was also suggested as the cause of walking impairment in the two demented patients reported by Rossor *et al*.⁶¹ In one of those patients, signs of Alzheimer's disease pathology were found at necropsy, and both patients

had clear medial frontal hypometabolism detected with positron emission tomography. The association between gait apraxia and mesial frontal lesions is in agreement with the body of observations of patients with stroke or tumour (for a review see Della Sala *et al* ⁶²).

In the current study, gait apraxia in Alzheimer's disease was associated with dementia severity. This ties in with the common clinical observation that severely affected patients may have great difficulty in walking,^{2 12 66} are stiff and clumsy in performing trunk movements, and when bedridden, are often hardly able to turn over in their bed. Gait apraxia is considered a sequel of mesial bilateral frontal damage.^{62 67} The observation of a clear correlation between AWS scores and the severity of dementia supports the hypothesis that gait apraxia may emerge when damage to the frontal areas of the brain appears later in the course of the disease. The progression of the neuronal degenerative process in Alzheimer's disease is maintained to follow a schematic three step pattern.^{11 18 68 69} The temporomedial encroachment is followed by the temporoparietal neocortical and, later, prefrontal involvement (reviewed by Spinnler⁷⁰). Deterioration of performance on the MODA parallels this progression.⁷¹ Thus it should not be surprising that the proportion of Alzheimer patients failing the AWS test increases with increasing severity, when the degenerative process is likely to involve the frontal lobes more extensively. This may not necessarily be the case, however, as shown by the lack of a significant correlation between the MODA and AWS scores in the patients who, on initial clinical examination, reported walking difficulties as a major symptom that were not accounted for by any other neurological disorder. These patients were the ones among the group who achieved the lowest scores on the AWS test.

Conclusions

Our study has shown first, that walking disorders in patients with Alzheimer's disease may result from gait apraxia; second, that the detection of gait apraxia is eased by the use of a standardised test, but still relies heavily on the exclusion of other causes of walking deficits; and third, that gait apraxia is a recognisable and independent form of apraxia.

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APPENDIX

Items contained in each component of the AWS test

Walking	
Examples:	Walk with right hand on stomach and left hand on back
	Walk with left hand on stomach and right hand on back
1	Walk on the spot
2	Walk forward
3	Walk with a wide stance (legs apart)
4	Walk to the right while facing forward
5	Walk crossing your legs over
6	Walk backwards
7	Walk with your feet diverging (pointing out)
8	Walk to the left while facing forward
9	Walk on your heels
10	Walk with feet converging (pointing in)
11	Walk with your trunk laterally bent to the left
12	Walk with your left arm stretched out and your right arm hanging by your side
13	Walk with arms folded
14	Walk with your trunk bent forward
15	Walk with your right arm stretched out and your left arm hanging by your side
16	Walk with your trunk laterally bent to the right
17	Walk with your hands behind the nape of your neck
18	Walk with your arms still alongside your trunk
19	Walk with your trunk extended backwards
20	Walk stepping over an imaginary obstacle
Trunk	
Examples:	Sit down (on the right edge of the bed)
	Sit on the edge of the bed
21	Anterior flexion of head
22	Rotate head to the left
23	Right lateral flexion
24	Posterior flexion
25	Rotate head to the right
26	Left lateral flexion
27	Anterior flexion of trunk
28	Shrug shoulders
29	Hold stomach in
30	Left lateral flexion of trunk
31	Posterior flexion of trunk
32	Right anterior flexion
33	Push stomach out
34	Sit down
35	Lie supine (starting from the right side of the bed)
36	Lie prone (starting from the right side of the bed)
37	Turn from prone to supine
38	Turn from supine to prone
39	Prone, get up
40	Lie supine (starting from the left side of the bed)
41	While supine, hug both knees
42	Lie prone (starting from the left edge of the bed)

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ECHO

Progression to malignancy in gliomas reflects inverse relation of PEDF and VEGF expression



Please visit the *Journal of Neurology, Neurosurgery, and Psychiatry* website [www.jnnp.com] for a link to the full text of this article.

A Chinese study has been the first to suggest that pigment epithelium derived factor (PEDF) expression is a marker for gliomas and might eventually be used to stop their growth.

PEDF mRNA in normal brain tissue was five times more abundant than in low grade malignant gliomas and over fifteen times more abundant than in high grade gliomas. It was significantly higher in low versus high grade gliomas. Cultured normal human glial cells were packed with PEDF protein whereas a glioma cell line (U251) was almost devoid of it. PEDF and vascular epithelial growth factor (VEGF) expression were inversely related in gliomas—PEDF expression progressively fell in transition from low to high stage malignancy as VEGF expression increased.

PEDF mRNA was measured by real time RT-PCR in surgical samples of normal brain tissue from patients with cerebral trauma (five) and 25 samples from patients with low grade (seven) and high grade (10) gliomas. PEDF and VEGF were immunostained with specific monoclonal antibodies in thin sections.

PEDF is a glycoprotein common to many tissues and found in almost all brain areas, which regulates growth and development in neural tissues. It has been implicated in inhibiting development of blood vessels and seems to protect neurones from tumour formation. So determining a relation between PEDF and VEGF—the most important stimulator of blood vessel development in solid tumours—was of special interest. Gliomas comprise 65% of primary malignant brain tumours, and their rapid growth and widespread vascularisation spells a poor prognosis.

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