SHORT REPORT

Cerebellar hypermetabolism in paraneoplastic cerebellar degeneration

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See Editorial Commentary, p 427

J Neurol Neurosurg Psychiatry 2006;**77**:525–528. doi: 10.1136/jnnp.2005.075325

A 51 year old man with paraneoplastic cerebellar degeneration from gastric adenocarcinoma showed cerebellar hypermetabolism and increased perfusion on brain FDG-PET scan and SPECT during the acute stage of his illness. The patient underwent subtotal gastrectomy. The intensity of the hypermetabolism had decreased markedly on follow-up FDG-PET 3 months later following two cycles of chemotherapy. We suggest that the cerebellar hypermetabolism may have been due to an acute inflammatory process associated with an immunological reaction.

Paraneoplastic cerebellar degeneration (PCD) is characterised by subacute onset of cerebellar dysfunction in patients with cancer.¹ Clinical features include ataxia of the limbs and trunk, gait imbalance, dysarthria, and nystagmus.^{1,2} Neurological manifestations may precede cancer symptoms in the majority of patients.^{1,2} Several antineuronal antibodies are found in the serum or cerebrospinal fluid (CSF) of patients with PCD, depending on the underlying tumour.¹ However, diagnosis remains a challenge when PCD occurs without onconeural antibodies. Although there have been a few studies on hypermetabolism in paraneoplastic limbic encephalitis,^{3,4} cerebellar hypermetabolism in patients with pure PCD has not been reported. We describe a man with PCD who showed cerebellar hypermetabolism and increased perfusion during the acute stage of his illness.

METHODS

Case report

A 51 year old man without previous medical illness was referred for investigation of vertigo, dysarthria, and severe gait imbalance. The symptoms had developed rather suddenly 2 weeks previously and subsequently remained stable. He had no headache and denied preceding infectious illness or exposure to toxic substances or heavy metals. On admission, his blood pressure was 130/80 mm Hg and he had a pulse rate of 79 beats per minute. Body temperature was 36.5°C. He was alert and had a full range of extraocular movements. There was no spontaneous or gaze evoked nystagmus. Saccades and smooth pursuit were normal. Transient counterclockwise torsional nystagmus (from the patient's point of view) was observed during both Hallpike manoeuvres. He had mild dysarthria and bilateral dysmetria in both arms and legs. Truncal sway and head titubation were evident while sitting. He was unable to stand without support. Routine laboratory analyses were normal. Serum tumour markers and serological tests for Epstein Barr virus and mycoplasma were negative. Chest x ray was normal. Lumbar puncture showed normal opening pressure, cell counts, glucose, and protein with negative cytology.

Brain MRI

MRI was performed using a 1.5 T system (Gyrosan Intera; Philips, Best, the Netherlands). Scans consisted of an axial T2 weighted fast spin echo sequence (TR/TE 4500/118 ms) and a T1 weighted sequence (TR/TE 400/8 ms) with 20 slices covering whole brain, 5 mm slice thickness, and 2 mm interslice gap. An axial diffusion trace sequence (single shot echo planar spin echo sequence, $b = 1000 \text{ s/mm}^2$, TR/TE 5000/139 ms), T1 weighted gadolinium enhanced sequence, and MR angiography were also obtained.

Brain and whole body FDG-PET scan

The patient fasted for 6 h prior to intravenous injection of 10 mCi (370 MBq) of fluorine-18 fluorodeoxyglucose. After injection, the patient was allowed to rest quietly in a dimly lit room for 30 min during the uptake phase. Whole body FDG-PET was performed using an Allegro PET scanner (Philips Medical Systems, Cleveland, OH). Brain imaging was performed by using an additional brain imaging pallet. For whole body imaging, 2.5 min emissions in nine table positions from the level of the proximal femur to the cerebellum and for brain imaging 10 min emissions in one table position were obtained in 3D acquisition mode. An attenuation map was obtained using a Cs-137 transmission source. Attenuation corrected images were reconstructed using a 3D-RAMLA (row-action maximum-likelihood) algorithm with a 3D image filter.

Regional activity in each image was normalised to the mean glucose metabolism in the whole brain as $20 \mu\text{mol/min/100 g}$ using proportional scaling. The normal value was derived from 12 age matched healthy men.

Brain SPECT

The subject was injected with 30 mCi of $^{99\text{m}}\text{Tc}$ -ethylcysteine dimer (Neurolite; Bristol-Myers-Squibb/Dupont Pharmaceuticals Boston, MA) under standard conditions of a dimly lit room, with eyes closed and minimal background noise. Scanning was initiated 30 min after injection using a dual head ADAC-Forte SPECT system (Philips Medical Systems) equipped with a low energy parallel-hole collimator. Acquisition was done over 25 min with 60 angles through 360° in step and shoot mode. Reconstruction was done using filtered backprojection with a Butterworth filter (order, 10; cut off, 0.30 cm^{-1}). Attenuation was corrected using Chang's method with an attenuation coefficient of 0.12 cm^{-1} . Regional activity was normalised to the mean blood flow in the whole brain as 50 ml/100 g/min (normal cerebellar blood flow $52 \pm 2 \text{ ml/100 g/min}$).

Abbreviations: CSF, cerebrospinal fluids; PCD, paraneoplastic cerebellar degeneration

RESULTS

Brain MRI

T2, T1, and diffusion weighted images showed no abnormal signal intensities in the cerebral hemispheres, brainstem, or cerebellum, and there was no abnormal enhancement on gadolinium enhanced sequences. MR angiography showed patent intracranial and extracranial arteries (fig 1A).

Brain and whole body FDG-PET

Brain and whole body FDG-PET scanning obtained 3 weeks after symptom onset disclosed significant hypermetabolism in the cerebellum, especially in the cerebellar vermis (mean cerebellar metabolic rate $59 \mu\text{mol}/100 \text{ g}/\text{min}$ in the patient v $39 \pm 3 \mu\text{mol}/100 \text{ g}/\text{min}$ in normal controls) (fig 1B, D) and hypermetabolic mass-like lesions in the distal antrum of the stomach (fig 2).

Brain SPECT

On brain perfusion SPECT obtained 3 weeks after symptom onset, hyperperfusion (mean blood flow $65 \text{ ml}/100 \text{ g}/\text{min}$ v

$52 \pm 2 \text{ ml}/100 \text{ g}/\text{min}$ in normal controls) was evident in both cerebellar hemispheres and vermis (fig 3).

Clinical course

Abdomen CT and gastroscopy revealed advanced gastric cancer and multiple lymph node enlargements without evidence of distant metastasis (fig 2C). Indirect immunofluorescence (triple tissue slide: mouse stomach, cerebellum, and kidney) and western blotting did not detect serum anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, or anti-mGluR1 antibodies.¹ The patient underwent subtotal gastrectomy (Billroth I) with radical excision of the lymph nodes. Histological examination of the mass disclosed adenocarcinoma (TNM stage IIIA). Three months later, following two cycles of chemotherapy with cisplatin and fluorouracil, the patient's imbalance showed slight improvement without signs of tumour recurrence. The intensity of hypermetabolism in the cerebellum was markedly reduced ($45.1 \mu\text{mol}/100 \text{ g}/\text{min}$) on follow-up FDG-PET 3 months later compared with the initial study (fig 1C).

Figure 1 (A) T2 weighted MRIs and MR angiography show no abnormal signal intensities in the cerebellum, and patent intracranial and extracranial arteries. (B) Transaxial and sagittal FDG-PET images of the patient, obtained 3 weeks after symptom onset, show increased uptake in the cerebellar hemisphere and vermis. (C) Cerebellar hypermetabolism has markedly reduced on follow-up scan 3 months later. (D) Representative images of normal brain FDG-PET taken from a 50 year old man are shown for comparison. The images were reoriented and resampled to have the same orientation as the patient's images.

Figure 2 (A, B) Whole body FDG-PET scan, obtained 3 weeks after symptom onset, disclosed hypermetabolic mass-like lesions in the distal antrum of the stomach and multiple hypermetabolic nodules in the perigastric and hepatic ligament area. (C) Corresponding slices from CT scan, taken 1 day after the initial PET study, also reveal enlarged metastatic lymph nodes.

DISCUSSION

The pathogenesis of paraneoplastic neurological syndromes including PCD is considered to be autoimmune mediated.² Onconeural antibodies react with both the cancer and the nervous system. These antibodies identify antigens which are normally present only in the nervous system but which are expressed ectopically in certain tumours for unknown reasons. Several antineuronal antibodies are found in the serum or CSF of patients with PCD depending on the underlying tumour. A recent study of 50 patients with PCD and antineuronal antibodies demonstrated that the most commonly associated tumours and antibodies were gynaecological and breast cancers (anti-Yo and anti-Ri), lung cancer (anti-Hu), and Hodgkin's lymphoma (anti-Tr and anti-mGluR1).¹ However, the association of PCD and gastric cancer is very rare. To the best of our knowledge, only three patients, one with anti-Yo associated PCD from gastric adenocarcinoma, another with anti-Ri antibody-positive PCD from neuroendocrine gastric carcinoma, and another with PCD from a malignant gastric carcinoid without

antineuronal antibodies, have been reported.⁵ Even though antineuronal antibodies were not detected, our patient met the definite diagnostic criteria of the paraneoplastic neurological syndromes proposed by Graus *et al.*⁶

Our patient showed hypermetabolism on FDG-PET scan and increased perfusion on SPECT in the cerebellum 3 weeks after the onset of his symptoms. The intensity of the hypermetabolism had decreased markedly on follow-up FDG-PET 3 months later. There has been no report on cerebellar hypermetabolism in pure PCD during the acute stage. In several patients with limbic encephalitis associated with malignancies, FDG-PET disclosed hypermetabolic foci in the medial temporal lobe during the acute stage.^{3,4} The authors attributed the hypermetabolism to inflammatory changes rather than seizure activity because there was no clinical or EEG evidence of seizures in the interictal state. Furthermore, stereotaxic biopsy in one of the patients revealed inflammation with lymphocytic infiltrations and reactive gliosis.³ Hence, in our patient, we also suggest that an acute inflammatory process associated with an immune

Figure 3 Transaxial and sagittal images of perfusion SPECT show increased perfusion in both cerebellar hemispheres and vermis, which is consistent with the cerebellar hypermetabolism shown on FDG-PET scan.

reaction may have given rise to hypermetabolism and hyperperfusion during the acute stage. Pathological studies of PCD also support the inflammatory theory: autopsy studies performed less than 1 year after the onset of neurological symptoms generally show severe but not complete loss of Purkinje cells in combination with various degrees of inflammatory, mainly lymphocytic, infiltrates. Studies performed more than 1 year after the onset of symptoms consistently show complete loss of Purkinje cells and absence of inflammatory infiltrates.^{7,8} In an earlier study, FDG-PET and SPECT, obtained 15 months after symptom onset, showed cerebellar hypometabolism and normal cerebellar perfusion in a patient with PCD.⁹ The long interval between symptom onset and the FDG-PET scan may explain the cerebellar hypometabolism and is consistent with the pathological studies.

Cerebellitis should be considered in the differential diagnosis of acute cerebellar dysfunction with normal brain MRI; hypermetabolism and hyperperfusion may be evident in the cerebellum on brain PET and SPECT during the acute stage.¹⁰ However, the lack of infectious signs, normal CSF findings, the presence of underlying tumours, and only partial improvement over the follow-up periods of several months led us to a diagnosis of PCD rather than cerebellitis.

Findings in our patient suggest that whole body and brain FDG-PET scan may be useful in the early diagnosis of PCD, especially in acute cerebellar syndromes with normal brain MRI and negative onconeural antibodies.

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This work was supported by a grant (R05-2001-000-00616-0) from the Korea Science and Engineering Foundation

Competing interests: none declared

Patient details are published with consent

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Received 3 July 2005

Revised version received 1 September 2005

Accepted 25 September 2005

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