LETTERS

Hypothalamic amnesia and frontal lobe function disorders after Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH), a rare disease previously known as histiocytosis X, is characterised by abnormal cell proliferation. If the CNS is invaded, the hypothalamus is the typical site location. There are virtually no neuropsychological data on hypothalamic LCH sequelae. Memory disorders in the context of posterior but also anterior hypothalamic lesions, regardless of the aetiology, have in most cases been attributed to the involvement of the mammillary bodies (MB). However, Ptak *et al* reinterpreted a case, acknowledging that "Damage of the anterior hypothalamus, rather than the mammillary bodies, may [. . .] have been responsible for [the observed] confabulatory amnesia" (page1600).[1] An interesting question is whether neuropsychological deficits are secondary to hypothalamic damage in itself or to a disconnection syndrome. The latter is based on the bilateral hypothalamic nucleus—widespread brain complex connections. Two subsystems are of particular interest in the present case, the hippocampus-fornix-hypothalamus-MB circuit, and the amygdalastria terminalis plus caudate nucleus-hypothalamus circuit.

We report the case of a patient who presented with hypothalamic LCH and underwent thorough neuropsychological, radiological, and metabolic assessments.

Case report

A right handed woman (date of birth 1931), was admitted (March 2000) to the Hôpitaux Universitaires' Neurology Unit (Strasbourg, France) complaining of memory deficits. In 1990, bronchopulmonary biopsies had led to the diagnosis of LCH. In 1992, she was diagnosed as having hepatic and hypothalamic LCH, the first being confirmed by biopsy, the seond suggested by diabetes insipidus. Endocrinological assessment showed signs of anterior pituitary dysfunction. Standard biological and physical examinations were normal. MRI showed a bilobulated hypothalamic tumour, extending from the optic chiasm to the posterior part of the third ventricle floor and towards the pituitary stalk. It displaced the left thalamus very slightly and compressed both MB, which became non-identifiable. There was no abnormal signal in the thalami and the mesial temporal regions were morphologically normal. Cortical atrophy was normal for her age. MRI follow up (1998, 2000, 2001), showed stable lesions (20×18×14 mm; fig 1). An ^{18}F fluorodeoxyglucose resting positron emission tomography (PET) scan (December 2000) revealed small hypometabolic regions in the ventromedial prefrontal cortices, left superior frontal gyrus, parietal lobe, caudate nucleus and upper brain stem, plus a pronounced hypothalamic hypermetabolism (fig 2).

Neuropsychological investigation (July 2000)
Written informed consent was obtained. The patient was disorientated for time only. Verbal IQ (90) and Performance IQ (96), language, constructional praxis, visuoperceptual, and spatial abilities were normal. Performance on anterograde and retrograde (episodic and semantic) memory tests was severely impaired. Likewise, scores on six tests sensitive to frontal lobe dysfunction were uniformly defective. Moreover, she had recently become "hostile and irritable". Consequently, her husband completed a personality change scale (J Barrash, *et al,* 25th INS meeting, Orlando, Florida, February 1997). The considerable difference between her past (63) and present (110) behavioural characteristics was compatible with a frontal lobe disorder.

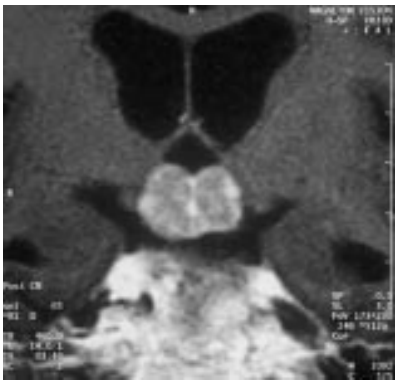

Figure 1 T1 weighted coronal MR image showing a circumscribed hypothalamic tumour.

Comment

Secondary to hypothalamic LCH, our patient developed amnesia, dysexecutive syndrome, and personality alteration, in an otherwise normal context.

Ptack *et al* described a similar case (amnesia and frontal lobe dysfunction) in the context of circumscribed hypothalamic lesions.[1] The postmortem diagnosis of sarcoidosis did not exclude the possibility of LCH. As the patient's lesion involved mostly the medial hypothalamus, the authors accounted for the symptoms in terms of the strong reciprocal connections with the anterior limbic structures. Further studies have demonstrated connections from the medial prefrontal cortex to the anterior and ventromedial hypothalamus and those from the orbital region to the lateral hypothalamus.[2]

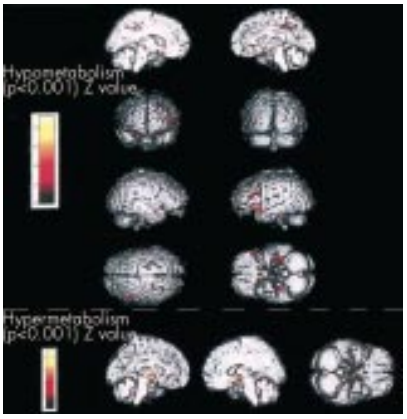

Figure 2 PET scan. Frontal, parietal, caudate nucleus, and upper brain stem hypometabolism, and hypothalamic hypermetabolism. Conditions were contrasted with 12 normal subjects (p<0.001).

In this case, the large lesion (optic chiasm, pituitary stalk, and MB), restricted to the hypothalamus, renders the findings particularly interesting in terms of hypothalamic connections. Given the evidence that LCH in this case is not an infiltrating but an encapsulated form of the disease, the small cortical zones of hypometabolism are not thought to be directly caused by the histiocytosis condition. They could be accounted for in terms of disconnections resulting from the hypothalamic lesion. The deficit in the memory consolidation process could reflect a dysfunction of the hippocampus-fornix-MB circuit. Failure of retrieval processes could reflect the prefrontal-hypothalamic connections. Moreover, the patient's false recognitions and confabulations showed the frontal involvement suggested by Ptak *et al*.[1] However, for the time being, we are unable to account for the parietal and upper brain stem hypometabolism.

The hypothalamic hypermetabolism is interpreted in terms of an index of the active ongoing disease process.[3]

In conclusion, we suggest that our patient's neuropsychological impairments, with their catastrophic consequences for daily life, require abnormality beyond the MB and might reflect the "superadditive" effect of damage at different, strategically important loci.[4] Indeed, theoretical considerations based on the mere "addition" of hypothalamic lesions plus a few very small hypometabolic zones at various sites in the brain would most probably not have predicted our patient's present cognitive status. Finally, given the paucity of hypothalamic LCH cases reported in the literature and the virtual absence of neuropsychological examination in those rare cases, the possibility of an as yet unknown specific effect of LCH on the CNS cannot be ruled out.

L Manning
LN2C (UMR 7521), Université Louis Pasteur, 12 rue Goethe, 67000 Strasbourg, France,

F Sellal
Service de Neurologie, Hôpitaux Universitaires, Strasbourg, France

Correspondence to: Dr L Manning; Lilianne.Manning@psycho-ulp.u-strasbg.fr

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Meningioma of the optic nerve sheath: treatment with hydroxyurea

The best treatment of optic nerve sheath meningiomas remains controversial. Recent reports have emphasised the efficacy of fractionated stereotactic or conformal radiotherapy, and some clinicians favour this approach instead of surgery or observation.[1 2] On the other hand, a beneficial effect of hydroxyurea on unresectable, residual, and recurrent meningiomas has been reported in

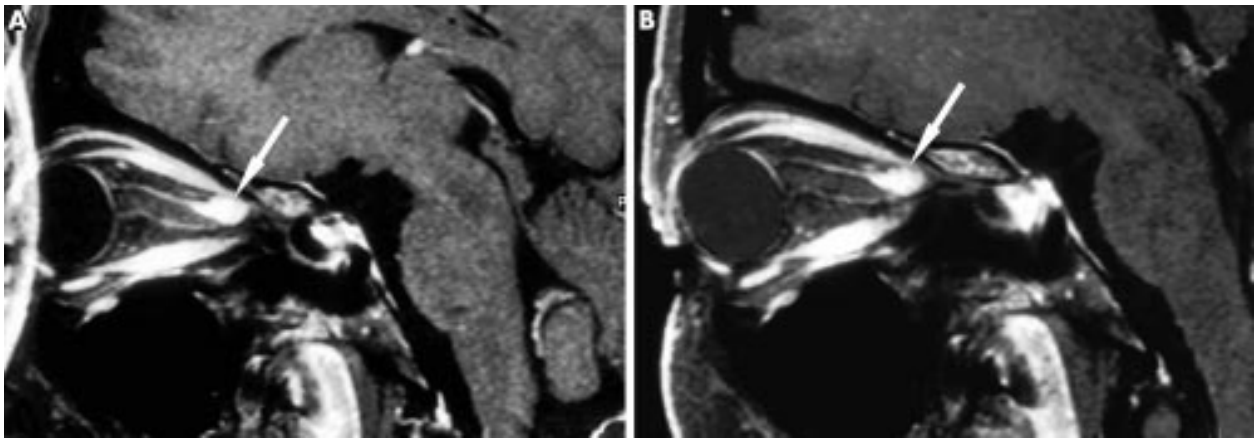

Figure 1 Sagittal T1 weighted magnetic resonance imaging, angulated along the course of the right optic nerve (time of repetition 500 ms, time of echo 16 ms, slice thickness 4 mm), following Gd-DTPA administration. It shows a homogeneously enhancing, 5 × 10 mm fusiform tumour, originating from the upper part of the right optic nerve sheath and compressing the nerve below.

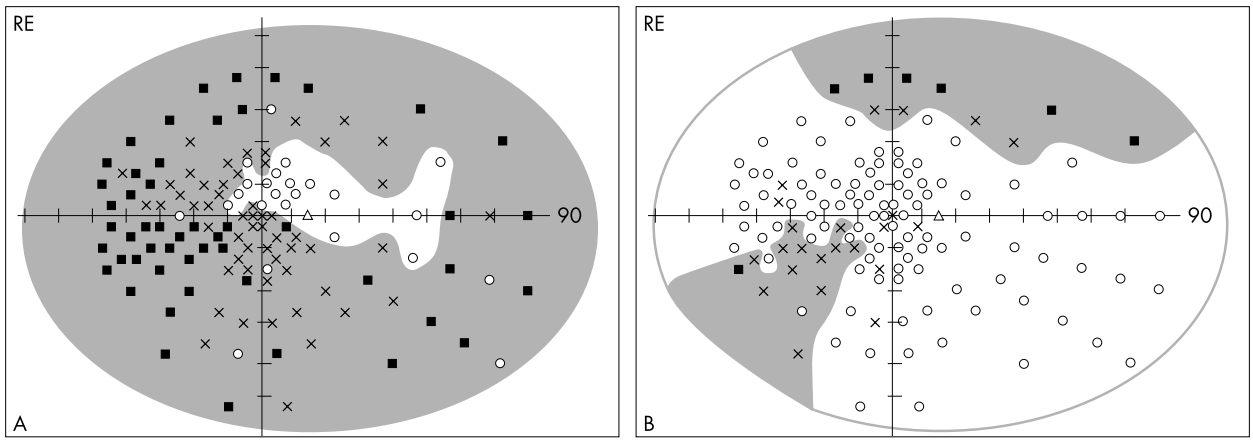

Figure 2 Computed perimetric examination of the right eye: (A) before treatment; (B) after 10 months of continuous treatment with hydroxyurea (20 mg/kg body weight/day). Black squares, absolute scotoma; crosses, relative scotoma.

various series.[3–5] We report a patient with a meningioma of the optic nerve sheath and nearly complete visual loss who was successfully treated with hydroxyurea alone.

Case report

A 46 year old woman presented with painless and progressive right sided visual failure for two years. On admittance, visual acuity of the right eye was 0.05. In addition, there was an afferent pupillary defect, and swelling of the optic disc. Otherwise, the neurological examination was normal. Cranial magnetic resonance imaging (MRI) revealed a homogeneously enhancing, fusiform tumour ($5 \times 10 \times 6$ mm; volume 0.15 cm^3) originating from the upper part of the right optic nerve sheath and compressing the optic nerve. The tumour showed an isointense signal to grey matter on T1 and T2 weighted images, and was diagnosed as a meningioma (fig 1A). Latency of the P100 wave of visual evoked potentials of the right eye was increased to > 200 ms, and computed perimetric examination showed a severe restriction of the peripheral visual field of the right eye (fig 2A). There were no clinical or radiological features of neurofibromatosis type 1 or 2. The patient was not on regular medication.

Treatment was initiated with hydroxyurea, 20 mg/kg body weight/day orally. Four months after initiation of treatment the patient reported a considerable improvement of vision. No adverse events were noted apart from mild hair loss. Visual acuity improved to 0.5. After seven months of continuous treatment, visual acuity was 0.7, and after 10 months, 0.8. At this time, P100 latency of visual evoked potentials was normal and computed perimetric examination showed a significant recovery of visual field (fig 2B). However, cranial MRI showed no detectable change in tumour size (volume 0.15 cm^3; fig 1B). At the time of writing the disease had remained stable for a further 18 months now.

Comment

This case shows the clinical value of hydroxyurea in the management of optic nerve sheath meningiomas, although there was no detectable decrease in tumour size. There is increasing evidence for the benefit of radiotherapy in optic nerve sheath meningiomas. Andrews *et al* reported an improvement in vision in 10 of 24 cases (42%) after treatment with fractionated stereotactic radiotherapy alone.[1] A comparison of long term visual outcome by Turbin *et al* showed better results for patients treated by conventional multiport or conformal planned delivery of radiotherapy than by surgery plus radiation, surgery alone, or observation during the follow up period.[2]

However, radiotherapy is associated with relevant treatment related morbidity (13% and 33.3% in two studies[1 2]). As follow up of the available case series is limited and these tumours may pursue a stable course for many years,[6] the appropriate time for therapeutic intervention is unclear. In the present case, a profound deterioration of visual acuity led to the initiation of treatment. Hydroxyurea may be a reasonable therapeutic alternative to radiotherapy. Side effects of hydroxyurea such as myelosuppression, raised liver enzymes, and rashes are generally mild, easy to monitor, and reversible.[4]

As the neuroradiological characteristics were unequivocal in our case, and as histological verification of optic nerve sheath meningiomas carries a high risk of irreversible damage to the optic nerve, the diagnosis was made purely by radiological means. This approach is in accordance with current standard of diagnostic measures of optic nerve sheath meningiomas based on clinical details and high quality neuroimaging without pathological confirmation.[1 2 6]

S Paus, T Klockgether, U Schlegel
Department of Neurology, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany

H Urbach
Department of Radiology, University of Bonn

Correspondence to: Professor Dr U Schlegel; uwe.schlegel@uni-bonn.de

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Recurrent anti-GQ1b IgG antibody syndrome showing different phenotypes in different periods

Anti-GQ1b IgG antibody is often found in the sera of patients with Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, Guillain–Barré syndrome with ophthalmoplegia, acute ophthalmoparesis without ataxia, and occasionally, in isolated internal ophthalmoplegia and chronic ophthalmoplegia.[1–3] These conditions may be designated as anti-GQ1b IgG antibody syndrome.[1] We report a patient who showed three different phenotypes of the anti-GQ1b IgG antibody syndrome at different periods.

Case report

The patient was a 19 year old woman. At age 10, she visited a neurologist because of diplopia and an unsteady gait two weeks after a respiratory tract infection. Neurological examination showed ophthalmoplegia, dilated pupils with sluggish pupillary responses, areflexia, and cerebellar ataxia. Laboratory findings including nerve conduction studies were normal except for a slight increase in CSF protein (40 mg/dl) without pleocytosis. Within three months, her condition gradually improved and she was discharged without a neurological deficit except for persistent areflexia.

At age 17, she noticed mild diplopia, which gradually got worse. She visited our hospital with the complaint of slowly progressive diplopia. Although ocular movements were not restricted, her pupils were dilated bilaterally with reaction to light. She showed areflexia and slight ataxia without pathological reflexes. Blood count, blood chemistry, and brain magnetic resonance imaging (MRI) were normal. Nerve conduction studies were normal except for absence of the F wave.

At age 19, a week after developing fever of unknown origin, the diplopia suddenly progressed. The next morning, her gait became unsteady and she was admitted to hospital. On admission (day 1), she had complete ophthalmoplegia without oculocephalic reflexes. The pupils were markedly dilated without reaction to light. Her speech was slurred. Her extremities were slightly weak. She could not sit on the bed by herself because of severe unsteadiness. Her deep tendon reflexes were absent, with no pathological reflexes. The CSF was normal, including the protein level. Nerve conduction studies were within the normal range except for absence of the F wave. An enzyme linked immunosorbent assay showed that serum IgG reacted strongly with GQ1b (titre, 1:3200) and GT1a (titre, 1:3200), but not with other gangliosides.

She was given intravenous immunoglobulin (IVIg) on days 2–6. On day 5, she developed disturbed consciousness, Cheyne–Stokes respiration, and extensor plantar responses. Intratracheal intubation was required for ventilatory failure. Electroencephalography (EEG) showed diffuse theta activity. Brain MRI was normal.

From day 11, her illness gradually improved. Serum anti-GQ1b IgG and anti-GT1a antibody titres decreased below the cut off level by day 55. The F wave on nerve conduction studies became normal by day 78. Fifteen weeks after the onset, she had almost recovered except for areflexia and slight restriction of ocular abduction of the both eyes.

Comment

Our patient showed three different conditions of the illness at three different periods between the ages 10 and 19: first, acute onset of ophthalmoplegia, ataxia, and areflexia at age 10, which is a typical presentation of the Miller Fisher syndrome; second, chronic progressive diplopia associated with internal ophthalmoplegia from age 17; and third, acute onset of complete ophthalmoplegia, ataxia, marked drowsiness, and respiratory paralysis with extensor plantar responses and EEG abnormalities at age 19.

We diagnosed the third episode as Bickerstaff's brain stem encephalitis, because she showed transient central nervous system involvement (drowsiness, respiratory disturbance, positive plantar responses, and EEG abnormalities) in addition to the triad of the Miller Fisher syndrome. High anti-GQ1b and anti-GT1a IgG antibody titres at the time of the most recent illness and their decrease following recovery supported this diagnosis.

There are clinical similarities between Miller Fisher syndrome and Bickerstaff's brain stem encephalitis, and these conditions have been considered as consecutive spectra of the same disease. Miller Fisher syndrome is usually a monophasic illness, but, on rare occasions, it may recur after a long asymptomatic interval.[4 5] It has been reported that clinical features of recurrent Miller Fisher syndrome are constant from episode to episode.[4 5] This is in contrast with recurrent Guillain–Barré syndrome, which shows considerable variety in the distribution and severity of weakness between each episode.[4] This is the first report of Bickerstaff's brain stem encephalitis as a recurrent episode of the Miller Fisher syndrome.

In the second phase of chronic progressive diplopia, our patient showed abnormalities of the pupils with slight ataxia and absence of the F wave in nerve conduction studies. As external ocular movement was not restricted, progressive diplopia might reflect pupillary abnormalities; diplopia has been discussed in isolated internal ophthalmoplegia without external ophthalmoplegia associated with anti-GQ1b IgG antibody.[2] In addition, chronic external ophthalmoplegia has been found with raised serum anti-GQ1b IgG antibody.[3] These findings suggest that chronic internal ophthalmoplegia may be associated with anti-GQ1b IgG antibody, although we could not examine this antibody during that period.

It is unique in our patient that three different phenotypes of the anti-GQ1b IgG antibody syndrome appeared at different times. There has up to now been no report in which different anti-GQ1b IgG antibody syndromes have recurred at different times in a single patient. Our case indicates that Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, and chronic internal ophthalmoplegia form part of the spectrum of the anti-GQ1b IgG syndrome, although the mechanism of the variability in clinical phenotypes of the anti-GQ1b IgG syndrome remains unknown.

In conclusion, our case indicates that different phenotypes of the anti-GQ1b IgG antibody syndrome can occur at different times in the same patient, showing that this syndrome may be a distinct entity with a wide clinical spectrum on a unique immunological background.

T Hamaguchi, K Yamaguchi, K Komai, M Yamada
Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi Ishikawa, Japan

H Yokoji, R Satake
Department of Neurology, Noto General Hospital, Japan

H Yoshino
Department of Neurology, Kohnodai Hospital, National Centre of Neurology and Psychiatry, Japan

Correspondence to: Dr Tsuyoshi Hamaguchi; gom56@med.kanazawa-u.ac.jp

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Sydenham's chorea may be a risk factor for drug induced parkinsonism

Sydenham's chorea, the most common cause of acquired chorea in childhood, is a delayed complication of group A β-haemolytic streptococcal infection.[1] It is thought to be caused by antibodies induced by streptococci which cross react with basal ganglia antigens.[2] Despite the decrease in Sydenham's chorea in developed countries, there is a renewed interest in this condition because of the hypothesis that a similar mechanism may play a role in the pathogenesis of a subset of patients with tics and other neuropsychiatric disorders.[3]

The treatment of Sydenham's chorea is based on the combination of penicillin and antichoreic drugs (valproic acid and/or dopamine antagonists). At the movement disorders clinic of the Federal University of Minas Gerais (MDC-UFMG), located in an area where Sydenham's chorea remains endemic, we have been struck by the occurrence of drug induced parkinsonism among patients with Sydenham's chorea. We therefore

decided to investigate the incidence of this complication in a cohort of patients with the condition, as well as in a group of subjects with Tourette's syndrome. The latter is an interesting choice for a control group as Tourette's syndrome and Sydenham's chorea share several clinical features—for example, childhood onset, the constellation of motor and behavioural disturbances, and the response to neuroleptic agents.[4]

Methods

In the first part of the study we undertook a retrospective review of the case records of patients with Sydenham's chorea and Tourette's syndrome followed up at the MDC-UFMG from July 1993 to October 2002, looking for drug induced parkinsonism. We then compared the chlorpromazine equivalent dose used in patients with Tourette's syndrome, Sydenham's chorea, and drug induced parkinsonism. For each patient with Sydenham's chorea we randomly selected two age matched subjects with Tourette's syndrome. Sydenham's chorea was diagnosed according to a modified Jones criteria,[1] and the *Diagnostic and Statistical Manual of Mental Diseases*, fourth edition (DSM-IV) criteria were used to identify patients with Tourette's syndrome. Drug induced parkinsonism was diagnosed when patients exposed to neuroleptics were found to have bradykinesia and at least one of the following: rigidity, tremor, postural instability. All patients were seen by one of us (FC). Differences were considered statistically significant at a probability (p) value of < 0.05.

Results

Sydenham's chorea was diagnosed in 91 patients and Tourette's syndrome in 97 during the study period. Five patients (5.5%) with Sydenham's chorea (mean (SD) age, 13.4 (2.1) years), of whom four were female, developed drug induced parkinsonism, whereas this complication was not identified in the Tourette's syndrome group ($p = 0.03$, Fisher's exact test). Parkinsonism was characterised by the presence of bradykinesia and rigidity in all five subjects, tremor was identified in three, and postural instability was not observed. The mean cumulative chlorpromazine equivalent dose used in the patients with Sydenham's chorea when they developed parkinsonism was 16 518 (6254) mg. The onset of drug induced parkinsonism occurred after a mean exposure of 88.2 (65.8) days.

The cumulative chlorpromazine equivalent dose in the 10 Tourette's syndrome patients (two female; mean age 13.5 (1.1) years ($p = 0.26$ *v* Sydenham's chorea)) during a three month period was 19 575 (6329) mg ($p = 0.76$ *v* Sydenham's chorea). At the time of the onset of drug induced parkinsonism the mean chlorpromazine equivalent dose in the Sydenham's chorea patients was 176.6 (95.5) mg; in the Tourette's syndrome group the figure was 217.5 (220.0) mg ($p = 0.05$, paired *t* test).

Comment

We showed that 5.5% of our patients with Sydenham's chorea developed drug induced parkinsonism during treatment with neuroleptics, while this complication was not observed in a cohort of Tourette's syndrome patients of the same body weight. There are several possible explanations for this. First, the patients with Sydenham's chorea might have received a higher dose of neuroleptics. This hypothesis is ruled out by the finding that 10 randomly selected, age matched Tourette's syndrome patients and the five Sydenham's chorea patients with drug induced parkinsonism were treated with a similar cumulative chlorpromazine equivalent dose during the three month period when the latter developed parkinsonism. One may argue that although both groups received a similar cumulative dose of neuroleptics in the time between the start of treatment and the onset of drug induced parkinsonism, the patients with Sydenham's chorea could have been exposed to a higher dose of dopamine receptor blocking drugs at the time when they developed parkinsonism. However, this was not the case because if anything the mean dose of neuroleptic in the Sydenham's chorea subjects at the onset of drug induced parkinsonism was lower than in the Tourette's syndrome patients, though the difference failed to reach statistical significance. A second explanation for our findings is the concomitant use of valproic acid in three of our Sydenham's chorea group. Although this drug has been implicated in the development of drug induced parkinsonism, this complication has only been described in adults treated for a period of 12 months or more.[5] A third and also unlikely hypothesis is the overrepresentation of female patients in the Sydenham's chorea group; however, recent studies have consistently failed to identify sex as a risk factor for drug induced parkinsonism.[6] Our results thus support the conclusion that in comparison with Tourette's syndrome, patients with Sydenham's chorea are at greater risk of developing drug induced parkinsonism.

Our study has limitations. First, it is a retrospective investigation of patients seen at a tertiary referral centre. This approach can lead to false positive associations, particularly in studies of disease clustering.[7] However, this limitation is minimised by the use of a control group of Tourette's syndrome patients referred to the MDC-UFMG by the same process. Second, we were not blinded to the clinical status of the patients. Although this would have been ideal, to have remained blinded to the diagnosis would have been impossible because of the obvious phenomenological differences between Sydenham's chorea and Tourette's syndrome.

We hypothesise that the increased susceptibility of patients with Sydenham's chorea to develop drug induced parkinsonism reflects an underlying nigro-striatal dysfunction produced by cross reactive streptococcus induced antibodies. Recent studies suggest that the antibodies circulating in the sera of Sydenham's chorea patients not only recognise antigens of the basal ganglia[2] but also CNS myelin, causing acute disseminated encephalomyelitis.[8] It is thus possible that the anti-basal ganglia antibodies also cross react with neurones of the substantia nigra.

The results of our study have two implications. First, there is a need for caution when treating patients with Sydenham's chorea with dopamine receptor blocking drugs. Second, as patients with Sydenham's chorea and Tourette's syndrome respond differently to neuroleptics, this weakens the hypothesis that similar mechanisms are involved in the pathogenesis of these conditions.

A L Teixeira, F Cardoso, D P Maia, M C Cunningham

Movement Disorders Clinic, The Federal University of Minas Gerais, Av Pasteur 89/1107, 30150-290 Belo Horizonte MG, Brazil

Correspondence to: Professor Francisco Cardoso; cardosof@metalink.com.br

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Comparison of the tendon and plantar strike methods of eliciting the ankle reflex

Little work has evaluated the various ways of eliciting the ankle reflex. A previous study of elderly patients with normal/absent reflexes found greater intraobserver and interobserver agreement with the plantar compared with the tendon strike method.[1] Other studies showed that the reflex was best elicited in the kneeling position but moving comatose patients can be impossible or lengthy.[2 3] We compared the reliability of the plantar and tendon strike methods of eliciting the ankle jerk in different disease states by examiners with different skill levels.

Four patients with pathologically brisk reflexes, five with reduced/absent reflexes, and nine subjects with normal ankle reflexes, as judged by an experienced neurologist, were recruited. All subjects had symmetrical signs and gave written informed consent. Subjects were screened from examiners so that only their legs were visible. None had identifying scars, wasting, or pes cavus. Subjects were examined by 15 third year medical students and five experienced neurologists. Initial training in both methods was given: in the tendon strike method the Achilles tendon of the supine patient was struck with the leg flexed at the knee and externally rotated at the hip; in the plantar technique the examiner's hand was struck while placed on the plantar aspect of a supine patient's foot. Reinforcement was permitted at examiners' discretion. Each examiner saw half of the subjects (that is, nine patients and controls) on four occasions. On each occasion they examined both ankles. Examiners evaluated the reflexes four times using each technique twice. The order of bed, subject, and method allocation to examiners was according to a randomised partially balanced incomplete block design. Examiners rated the reflexes as normal, pathologically brisk, or reduced/absent and stated whether or not they were confident in their result. The study had local ethical approval.

Table 1 (A) Sensitivity of tendon and plantar strike methods including κ coefficient of interobserver agreement. (B) Intraobserver agreement between two tests of each method shown as the percentage (95% CI) of times that identical results were obtained. The κ coefficient (standard error) shows response agreement for the two test sessions for each method

A		% Correct reduced/absent (95% CI)	% Correct normal (95% CI)	% Correct brisk (95% CI)	κ (SE)
Students	Tendon strike	81.1 (64.8 to 92.0)	57.7 (45.4 to 69.4)	37.0 (19.4 to 57.6)	0.36 (0.06)
	Plantar strike	89.2 (74.6 to 97.0)	54.9 (42.7 to 66.8)	70.4 (49.8 to 86.2)	0.50 (0.06)
Clinicians	Tendon strike	92.3 (64.0 to 99.8)	63.2 (38.4 to 83.7)	61.5 (31.6 to 86.1)	0.56 (0.10)
	Plantar strike	92.3 (64.0 to 99.8)	63.2 (38.4 to 83.7)	61.5 (31.6 to 86.1)	0.57 (0.10)
B		**Subjects reduced/absent**	**Subjects normal**	**Subjects brisk**	**κ (SE)**
Students	Tendon 1st and 2nd	86.5 (71.2 to 95.5)	67.6 (55.4 to 78.2)	66.7 (46.0 to 83.5)	0.53 (0.07)
	Plantar 1st and 2nd	81.1 (64.8 to 92.0)	64.8 (52.5 to 75.8)	59.3 (38.8 to 77.6)	0.51 (0.06)
Clinicians	Tendon 1st and 2nd	92.3 (64.0 to 99.8)	68.4 (43.4 to 87.4)	61.5 (31.6 to 86.1)	0.59 (0.10)
	Plantar 1st and 2nd	92.3 (64.0 to 99.8)	57.9 (33.5 to 79.7)	92.3 (64.0 to 99.8)	0.66 (0.09)

Table 1A shows the sensitivities for the first of examiners' encounters with each subject/method. Sensitivity was high for the reduced/absent category for both experience levels, but low for normal or increased reflexes. The tendon method for students on brisk reflex patients was particularly inaccurate compared with plantar. This was not true for clinicians. Despite low sensitivity, examiners sometimes declared confidence in their incorrect classifications: 81% declared confidence when incorrectly classifying a brisk reflex using plantar compared with 63% using the tendon method. Intraobserver agreement for reduced reflexes was reasonable but lower for normal or brisk (table 1B). These were not always small misclassification errors: 23% of clinicians' test pairs using tendon strike classified an increased reflex correctly once but as absent on the other test. In several instances the reflex was incorrectly classified on both tests. All 13 students who declared a preference preferred the plantar strike but no clinician stated a preference.

We found poor sensitivity and reproducibility for both techniques with normal and brisk reflexes for both examiner types. Results for reduced/absent reflexes may be inflated as most patients had absent reflexes which are easier to detect. Also they may have had other subtle lower motor neurone signs giving clues to examiners. The low sensitivities show that the ankle reflex should be interpreted in the light of other physical signs. Experienced clinicians had similar results with both techniques. This conflicts with previous findings in elderly patients with normal or reduced reflexes of better interobserver and intraobserver agreement with the plantar method.[1] The disparity may reflect this study including patients with brisk reflexes or that the clinicians were neurologists, or both. Medical students did better with the plantar method for brisk reflex patients. They have insufficient experience to differentiate normal from brisk with the tendon method. This suggests that students should be taught the plantar method in preference to the tendon strike method.

C E Clarke, P Davies, T Wilson, T Nutbeam
Department of Neurology, City Hospital, Birmingham, UK

Correspondence to: Dr C E Clarke, Department of Neurology, City Hospital, Dudley Road, Birmingham B18 7QH, UK; c.e.clarke@bham.ac.uk

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Mirror movements of the non-affected hand in hemiparkinsonian patients: a reflection of ipsilateral motor overactivity?

Mirror movements may result from a primary motor efferent system dysfunction with secondary motor reorganisation. A profound dysfunction of the motor pathways has been reported in Parkinson's disease (PD) during execution of motor tasks.[1 2] Recent PET studies have demonstrated overactivation of ipsilateral motor areas in hemiparkinsonian patients.[3 4] However, the clinical expression of ipsilateral cortical activation was not specifically investigated in previous reports. In this study, we explored the presence of mirror movements (MM) during standardised unilateral hand tasks in a series of 21 hemiparkinsonian patients.

Patients were divided into two groups: de novo patients (n=11), age 53.2 (7.5) years (mean (SD)), duration of evolution 1.8 years (range: 1–5 years), UPDRS III motor score 12 (5.7), affected side: left n=5, right n=6; and treated patients (n=10), age 59.8 (7.6) years, duration of evolution 3.7 (1.8) years (range: 2–7 years), UPDRS III motor score 14 (7.5), affected side: left n=4, right n=6, mean daily dose of levodopa: 450 mg (range: 300–900 mg), improvement of motor disability >40% (range: 40%–80%). Evaluation was performed as follows: for de novo patients, before treatment; for the treated patients, in the "off" condition after at least 12 hours withdrawal of antiparkinsonian treatment (levodopa). Patients were not tested in the "on" condition, to avoid confusion between dyskinesia and MM. They were compared with 21 age matched normal subjects, age 56.4 (10.8) years.

Activation tasks

Subjects were told to hold their hands in the air with the elbows flexed and to perform a voluntary movement with one hand while the other hand was relaxed. Each hand was tested separately in the following four tasks performed 10 times as rapidly as possible with the widest amplitude: (1) pronosupination movements, (2) opening and closing of the hand, (3) finger tapping (thumb and index finger), (4) flexion-extension movements of the wrist. Tasks 1 to 3 correspond to items 23 to 25 of the UPDRS III, respectively.

Each task was scores as follows: 0= no MM, 1=MM (that is, the presence of repetitive unintentional contralateral movements that mimic totally or partially the intended movement. The "MM score" was the combined score for the task, for each side (maximum 4). Statistical analysis was performed using the non-parametric Spearman test, for a correlation analysis between the "MM score" and the UPDRS motor score.

In 80% of the de novo patients and 90% of the already treated and more severely affected patients, tested in the "off" condition, MM were observed in the relaxed hand while voluntary movements were being performed with the other hand. The most remarkable finding was that MM were never observed when voluntary movements were performed with the non-affected hand, whereas they were almost constant when voluntary movements were performed with the affected hand. They were observed both in the de novo group and the treated group. There were more often observed for alternate movements or repetitive flexion/extension movements of the wrist than for finger tapping. None of the control subjects displayed MM.

In the de novo patients, there was a significant correlation (r=0.60; p=0.0475) between the severity of motor impairment, as defined by the UPDRS III motor score, and the occurrence of MM as indicated by the "MM score". No such correlation existed in the treated group.

Mirror movements could reflect the higher than normal level of cerebral activation in response to complex movements reported both in normal subjects[2] and in PD patients.[1–3] However, none of the controls displayed MM and the four tasks were not complex as patients performed them without difficulty, albeit more slowly.

Alternatively, extended recruitment of cortical motor areas could reflect an overflow of commands into the contralateral hemisphere in unilaterally affected patients. In line with recent experimental results in a unilateral rodent model of Parkinson's disease,[5] and in patients,[2 3] we suggest that MM observed in the non-involved hand during movements of the akinetic hand reflect ipsilateral activation of the primary motor cortex.[3 4] In the absence of sensorimotor activation controlateral to the affected akinetic (right) hand, the ipsilateral diffusion of activation may be considered as a compensatory mechanism.[3] This ipsilateral activation could be explained in two different ways. Firstly, a corticocortical spread as the two hemispheres are connected via the corpus callosum and corticocortical pathways. Secondly, bilateral basal ganglia projections as several anatomical observations have shown that the basal ganglia are reciprocally and directly connected to the contralateral cortex.[6] Thus, the activation of the ipsilateral motor cortex could result from the activation of one or both of these pathways. The precise role of the ipsilateral activation of the primary cortex in the pathophysiology of Parkinson's disease is still unknown but it could be suggested that this phenomenon is a compensatory mechanism.

J S Vidal, P Derkinderen, M Vidailhet
Department of Neurology, Hôpital Saint-Antoine, Paris, France

S Thobois, E Broussolle
Department of Neurology, Neurological Hospital Pierre Wertheimer, Lyon, France

Correspondence to: Dr M Vidailhet, Service de Neurologie, Hôpital Saint Antoine, 184 rue du faubourg Saint-Antoine, 75012 Paris, France; marie.vidailhet@sat.ap-hop-paris.fr

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PostScript

CORRESPONDENCE

The harsh realities facing the use of SPECT imaging in monitoring disease progression in Parkinson's disease

Dr Snow is right to be cautious in his optimism concerning the use of functional imaging markers in neuroprotection studies in Parkinson's disease[1] as storm clouds gather[2 3] over the methods and interpretation of CALM-PD and REAL-PET. The concerns, however, are not limited to the effect of drug treatment on ligand uptake. Most importantly we need to ask the weight that should be placed on the result of functional imaging studies when they are not supported by the accompanying clinical data. In addition, there are concerns about the ability of the methods for accurately monitoring progression. The key requirements for a PET or SPECT method to be used in assessing progression are sensitivity to clinical change and reproducibility.[4] There are no data concerning either from the study of Winogrodzka and colleagues,[5] the authors quoting reproducibility data from Seibyl *et al*.[6] These data need to be presented for the benefit of the readership. The mean (SD) scan to scan variability in a group (n = 7) of patients with Parkinson's disease was 16.8 (13.3)%. It is surely only in functional imaging that a measurement to measurement variability of ±43% (mean ± 2 SD) could be described as highly reproducible[5] or excellent.[6] Sensitivity provides knowledge of the amount a functional imaging marker will change with a given clinical change, and I have yet to be convinced (partly because the data have not been presented) that [^{123}I]B-CIT SPECT can provide the necessary sensitivity to outweigh the very strong influence of scan to scan variability. The problems are compounded in studies of L-dopa versus agonist because within the first year a significant number of patients will leave the study or require supplementary L-dopa. The data of Winogrodzka and colleagues[5] illustrate this. In one year mean scan to scan change because of progression is 8% of baseline (or about 4% of normal mean), where mean (SD) scan to scan variability (which may be biological or methodological) is 16.8 (13.3)%. If we are looking for a 25% difference in rate of progression between the two study arms over one year (a difference of 2% progression from baseline) we need a technique that gives a more reproducible measurement than ±43%. This is the principal problem that needs to be addressed before further ''neuroprotection'' studies take place using [^{123}I]B-CIT SPECT.

P K Morrish
Hurstwood Park Neurological Centre, Princess Royal Hospital, Haywards Heath, East Sussex; paul.morrish@bsuh.nhs.uk

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Authors' reply

We would like to thank Dr Morrish for his comments on our paper.[1] We agree that it would be of interest to present the data of the longitudinal progression of dopaminergic degeneration (as measured by [^{123}I]β-CIT SPECT) in correlation with data on clinical progression. In our study, the patients were drug-naive when the baseline SPECT scans were obtained. Interestingly, these SPECT data correlated highly with clinical scores (motor UPDRS), which indicate that the SPECT measures may be of value in monitoring progress of nigrostriatal degeneration. Within our study design, however, the patients did not discontinue their dopaminergic drug treatment when the second [^{123}I]β-CIT SPECT scan was done (one year after baseline). Consequently, the UPDRS scores were influenced by dopaminergic drug effects and therefore were not suitable to study correlations with [^{123}I]β-CIT SPECT measures. Nevertheless, as dopamine transporter imaging will only be a relevant tool for monitoring dopaminergic degeneration if it ultimately reflects meaningful changes in clinical function in patients with Parkinson's disease, future studies should investigate this relation carefully. However, there is still debate on how adequate clinical data can be obtained in patients on drug treatment. For example, it is still unclear whether data obtained in the ''defined OFF stage'' are adequate enough to assess clinical progression (for a discussion, see Marek *et al*, 2003[2]).

Concerning the issue of variability and reproducibility of the [^{123}I]β-CIT SPECT technique, we of course agree with Dr Morrish that, for the benefit of future neuroprotection studies, all effort should be made to improve analysis methodology to reduce the variance in imaging outcomes. Variability may be reduced, for example, by quantifying radioligand binding automatically on a voxel by voxel basis (three dimensional).[3] Moreover, to reduce variability in SPECT measures for dopamine transporter binding, other tracers than β-CIT might be of value. For example, FP-CIT SPECT studies in patients with Parkinson's disease have shown reproducibility of the order of 8%.[4] This high reproducibility may stem from the fact that acquisition can be started as soon as three hours after injection for [^{123}I]FP-CIT,[5] whereas the optimal time point for acquisition of [^{123}I]β-CIT studies is 20 to 24 hours after injection. Consequently, the counts statistics are better for [^{123}I]FP-CIT than for [^{123}I]β-CIT SPECT studies. Interestingly, a recent preliminary study showed the feasibility of using [^{123}I]FP-CIT SPECT for monitoring dopaminergic degeneration in Parkinson's disease.[6] Nevertheless, it would be of major importance that further studies focus on minimising the variability in SPECT measures of dopamine transporter binding, and show which radiotracer is optimal for performing progression studies.

A Winogrodzka, J Booij, E Ch Wolters
Department of Neurology, Vrije Universiteit Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Correspondence to: Dr A Winogrodzka; a.winogrodzka@vumc.nl

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CORRECTIONS

There were two mistakes published in the table of the short report, Sjögren's syndrome associated painful sensory neuropathy without sensory ataxia, by K Mori, M Iijima, M Surgiura *et al* in the September issue of *JNNP* (2003;**74**:1320–2): the digit 9 was added to the eleventh column head by accident and the second entry in the final column should read 12, not 2.

The authors of the letter entitled Meningioma of the optic nerve sheath: treatment with hydroxyurea, published in the September issue of JNNP (2003;**74**:1348–50) were listed in the incorrect order. The author order should read as follows: S Paus, T Klockgether, H Urbach, U Schlegel.