PostScript

LETTERS

Mirror movements in Parkinson's disease: effect of dopaminergic drugs

Mirror movements refer to involuntary movements that emulate voluntary activity in contralateral homologous body regions.¹ We recently described this phenomenon in the less affected limb in early asymmetric idiopathic Parkinsonism.² The effects of time and dopaminergic drugs have not been examined. We now report on the re-evaluation of this clinical sign in a subset of patients with clinically definite Parkinson's disease who were undergoing dopamine replacement therapy, from our original cohort.

Methods

We recruited 13 treated patients for this longitudinal assessment from the initial cohort of 27 patients² with suspected mirror movements and recent-onset asymmetric idiopathic Parkinson's disease, seen at the Movement Disorders Centre, Toronto Western Hospital, between September 2001 and January 2003. At follow-up, all patients had been receiving optimal doses of dopaminergic drugs for many months. Parkinsonian features were combined into axial and lateralised scores using related items of the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS). The asymmetry index was calculated as the absolute difference between the sides divided by the sum of their scores ($(L-R)/(L+R)$). A larger asymmetry index indicates greater difference in disease burden between sides

and therefore more asymmetry. The patients' total daily dose of dopaminergic drugs were converted to levodopa equivalents using a published formula.³ The evaluation was first performed at least 12 h after the last dopaminergic treatment ("off" condition), and immediately after obtaining maximal benefit after intake of the first morning dose of dopaminergic treatment ("on" condition) given as immediate-release carbidopa-levodopa preparation in levodopa equivalent dosages.³ The four assessed tasks performed corresponded to UPDRS items 23 (finger tapping), 24 (hand movements), 25 (forearm pronation-supination) and 26 (foot tapping). These tasks were videotaped with a standardised protocol. Two investigators, blinded to the study, rated the associated mirror movements in amplitude, distribution and proportion of mirroring activity using our previously published clinical scale.² Simple and multiple linear regressions were used to test the effects of UPDRS total motor, axial, limb composite and lateralised scores on mirror movements. We evaluated changes in UPDRS and mirror scores with time and drugs using repeated-measures analysis of variance, paired t test or sign-ranked test as appropriate. Agreement between clinicians (inter-rater reliability) was measured using the κ statistic.⁴ κ levels were interpreted as follows: <0.4, poor to fair agreement; 0.4–0.6, moderate agreement; 0.6–0.8, substantial agreement and >0.8, excellent ("almost perfect") agreement.⁵ Data were analysed using StatView V.5.01 (SAS Institute, Cary, North Carolina, USA).

Results

The inter-rater reliability for the raters blinded to the study was substantial for off

and on assessments with chance corrected κ scores of 0.76 and 0.75, respectively. Table 1 lists the clinical and mirror movement features of the 13 patients (eight women) assessed. Tremors was the initial symptoms for most (10/13) of the patients. The side and nature of initial deficits, age and sex had no influence on mirror movement score, disease duration and UPDRS score. None of the patients had mirror movements on the more affected side. Table 1 shows the distribution of mirror movements. The mean time between the two assessments was 2.8 years (SD 0.8). At the second assessment, all patients were on dopaminergic treatment with a levodopa equivalent of 529 mg (SD 295). The off and on mirror movement scores were not significantly different from the first assessment. Among the independent predictors used for the assessments (table 1), the only significant difference was between UPDRS off and on scores ($p < 0.001$). Therefore, we examined whether the changes in UPDRS scores correlated with changes in mirror movements. We found a highly significant inverse correlation between UPDRS change (UPDRS off–UPDRS on) and mirror movement change (mirror movements off–mirror movements on) ($r = 0.83$; $p = 0.002$). From off to on, patients with large improvement in UPDRS scores had more mirror movements whereas those with small improvement in UPDRS scores had less mirror movements (fig 1). Higher levodopa equivalents tended to be associated with more mirroring ($F = 2.56$; $p = 0.138$), but this trend was lost when adjusted for motor UPDRS scores. The asymmetry index predicted the severity of mirroring on the less affected or unaffected side in a linear fashion at initial assessment ($r = 0.63$; $p = 0.02$) but not during off ($r = 0.07$; $p = 0.809$) or on states ($r = 0.07$; $p = 0.820$) at the second assessment.

Comments

We confirmed that mirror movements in the less affected limb are a feature of Parkinson's disease. They persist beyond 5 years of disease evolution, for at least 2–3 years after dopaminergic treatment is initiated, and their association with asymmetry is restricted to the earliest stages of clinical disease. Once treatment is started, the severity of mirror movements is influenced by dopaminergic drugs; mirroring was more prominent in patients whose motor response to dopaminergic treatment was greatest and less prominent in those whose response was less overt.

Although there was no overall change in mirror movement from the off to the on assessment, the inverse correlation between changes in UPDRS and mirror movements is intriguing. The reason for this correlation is not known. We speculate that in patients with large motor improvement, the improvement in bradykinesia and rigidity on the less affected arm may allow more mirror movements to occur. Although levodopa-induced dyskinesia may increase with voluntary movement, none of our patients had dyskinesia and this is unlikely to be a contributing factor. Moreover, levodopa-induced dyskinesia usually develops first on the most affected

Table 1 Characteristics of patients and mirror movements

	At first assessment	At second assessment
Age (years)	63.4 (8.6, 43 to 78)	66.0 (8.4, 46 to 80)
Disease duration (years)	2.7 (1.4, 0.8 to 5.5)	5.5 (1.6, 3 to 9)
Levodopa equivalents (mg)*	46.4 (97.0, 0 to 300)	528.9 (294.7, 150 to 1000)
Motor UPDRS	21.3 (6.0, 9.5 to 28.5)	Off: 22.2 (8.9, 12.0 to 35.5) On: 17.2 (9.1, 7.0 to 29.5)
Lateralised UPDRS†	7.2 (3.2, 2 to 12)	Off: 6.0 (3.1, 3 to 11) On: 4.2 (1.8, 2 to 7)
Asymmetry index	0.50 (0.30, 0.12 to 1)	Off: 0.36 (0.21, 0 to 0.62) On: 0.38 (0.16, 0.14 to 0.67)
Axial UPDRS	6.7 (2.8, 3 to 12)	Off: 8.8 (5.2, 1 to 18) On: 7.7 (5.4, 0 to 16)
Mirror movement total score	13.4 (8.2, 0 to 25)	Off: 10.7 (8.2, 0 to 31) On: 11.4 (8.8, 0 to 23)
Distribution of mirror movements: (n/13)		
Hands only	4	Off: 4 On: 6
Foot only	1	Off: 1 On: 6
Foot and hand	6	Off: 7 On: 5
No mirror movements‡	2	Off: 1 On: 1

Values in parentheses are SD, range.

UPDRS, Unified Parkinson's Disease Rating Scale.

*Only three patients were treated at first assessment, all were treated at the second assessment.

†Absolute side differences.

‡On the basis of video scoring these patients were found to have no mirror movements.

Figure 1 Regression plot of change in Unified Parkinson's Disease Rating Scale (UPDRS) and mirror movement (MM) scores. The horizontal line represents no change in MM. A negative change in MM indicates more mirroring and a positive change in MM indicates less mirroring.

side,⁶ contralateral to the mirroring limb. In patients with small motor improvement, most of the treatment benefit may be on the more affected side. The reduction in mirror movements may be due to a reduced degree of asymmetry or a reduction in the effort required to perform the tasks used to assess mirror movements.

The potential use of mirror movements in the clinical evaluation of disease progression and the complete characterisation of the effects of dopaminergic dosage will require further studies with longer washout periods. Our mirror movement scale possesses substantial inter-rater reliability for carrying out this objective.

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Cerebrospinal fluid findings in multiple sclerosis patients before, during and after pregnancy

The mechanisms responsible for the lower relapse rate of multiple sclerosis during pregnancy and an increased relapse rate during the postpartum period are still undefined. Putative explanations include pregnancy-related alterations in the function of the immune system, such as a shift towards T helper (Th)2-type immune reactivity and expansion of regulatory T lymphocytes.^{1,2} Analysis of the cerebrospinal fluid (CSF) offers a unique opportunity to characterise immunological pathways in the pathogenesis of multiple sclerosis. The inflammatory activity in the central nervous system (CNS) of patients with multiple sclerosis is reflected in the composition of CSF cells and one hallmark of the disease is the production of intrathecal antibodies. The aim of our study was to investigate the alterations that take place in the CSF of patients with multiple sclerosis during pregnancy. To our knowledge, no previous attempts have been made to analyse the components of the CSF of pregnant patients with multiple sclerosis.

Methods

The study included six patients with relapsing remitting multiple sclerosis, who were enrolled at a time of known pregnancy status.

Follow-up with recording of relapses continued until 6 months after the delivery. Only one of the patients (case 5) was undergoing disease-modifying treatment (subcutaneous interferon (IFN)- β 1a) before pregnancy, and the drug was discontinued 3 months before the onset of pregnancy. No immunomodulatory treatment was used during pregnancy or postpartum at the time of drawing the sample. All but one patient (case 4) chose to breast-feed (duration range 6 weeks to 6 months). There were no signs of postpartum depression in any of the patients. One CSF sample was drawn at 26–28 weeks of pregnancy, at a time of putative low disease activity. The second CSF sample was drawn 4–5 weeks after the delivery, at a time of putative high disease activity. Lymphocyte number, IgG-Index and number of oligoclonal bands were analysed from the CSF. At the same time points, venepuncture was performed for peripheral blood lymphocyte isolation and immunofluorescence staining for intracytoplasmic IFN- γ and interleukin (IL)-4 production, which was performed as described earlier.³ The study was approved by the Commission of Ethics of Turku University and the Turku University Central Hospital, and informed consent was obtained from all subjects after a full explanation of the procedure. A lumbar puncture is a standard procedure during diagnostic investigation in Finland and hence is performed often. All patients were fully aware of the scientific nature of the lumbar puncture, and were still willing to give the samples for analysis as accepted by the ethical committee.

Analysis of variance for repeated measurements and Newman–Keuls multiple comparison post-test were used for comparisons of the relapse rate and the differences in the IgG indices. The Expanded Disability Status Scale values were compared by using a paired, two-sided t test.

Results

Six women with definite relapsing remitting multiple sclerosis and a known pregnancy status were studied. The duration of the disease was 1–11 years (range) and the mean (SD) age of the patients was 26 (5) years. During the year before pregnancy, the relapse rate was 1 (0.9) relapses/patient/year (mean (SD)). During pregnancy, only one of the patients experienced a relapse; this was during the first trimester. In the 6-month postpartum period, all but one patient experienced a relapse (relapse rate during pregnancy v postpartum: 0.2 (0.6) v 1.7 (0.9); $p = 0.0336$). The Expanded Disability Status Scale was 1.2

Table 1 CSF findings

Patient	Before pregnancy		During pregnancy			After pregnancy		
	IgG-Ind	Cells	IgG-Ind	Cells	OB	IgG-Ind	Cells	OB
1	0.76	4	0.77	0	0	0.69	8	0
2	0.71	12	0.80	1	1–2	0.67	2	1–2
3	3.18	ND	4.77	0	3–4	4.06	4	3–4
4	2.28	26	3.19	1	1–2	2.08	9	1–2
5	1.22	12	2.19	2	1–2	1.14	2	1–2
6	0.70	0	0.74	0	0	0.72	8	0

Before pregnancy, diagnostic lumbar puncture; during pregnancy, at 26–28 gestational weeks; after pregnancy, 4–5 weeks postpartum; IgG-Ind, IgG-Index; cells, number of lymphocytes $\times 10^6$ /l. Cell number is in bold if sampling was performed during a relapse; OB, number of oligoclonal bands, was determined by using the Paragon Protein (SPE-II) Electrophoresis Kit, Beckman Coulter, Fullerton, California, USA. ND, not detected.