ORIGINAL ARTICLE

Prognosis of Japanese encephalitis patients with dystonia compared to those with parkinsonian features only

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Objectives: A number of movement disorders have been reported in Japanese encephalitis (JE). The prognostic significance of these movement disorders, however, has not been evaluated. The present study reports the prognostic significance of parkinsonian features and dystonia in JE.

Patients and methods: During 1992 and 1998, 50 JE patients were managed; 35 of them developed movement disorders (the study group). The diagnosis of JE was based on clinical, radiological, and serological criteria. Parkinsonian features were rated by the unified Parkinson's disease rating scale and dystonia by the dystonia rating scale. The patients with parkinsonian features only were classified into group I and those with additional dystonia or dyskinesia into group II. The outcome was defined at the end of three months into poor, partial, and complete recovery depending on how the patients coped with daily living activities.

Results: The patients' ages ranged from 2 to 64 years and 11 were females. The admission mean Glasgow coma scale score was 6.9 (range 4–13). The movement disorders were noted after 1–4 weeks of ictus. There were 16 patients in group I and 19 in group II. The parkinsonian features were more pronounced in group II than in group I. At three months of follow up, fewer patients had parkinsonian features in group I than group II. Hypophonia, however, persisted in 12 patients in group I and 16 in group II until the three month follow up. In group II, the mean dystonia score was 3.2 which regressed to 1.8 at three months. Tremor was present in five patients in groups I and eight in group II. Cranial computed tomography was abnormal in six and magnetic resonance imaging abnormal in 15 patients in group I and in nine and 12 patients respectively in group II. The thalamus was most frequently involved (11 patients in each group), basal ganglia (four in group I and six in group II), and midbrain (six in group I and one in group II). Group II patients had poorer recovery compared with group I. In group I, at the end of three months functional recovery was complete in 10, partial in two, and poor in three patients. In group II, four patients had complete, seven partial, and eight poor recovery.

Conclusion: JE results in a transient form of parkinsonian syndrome, which is associated with a lower frequency of tremor and prominent hypophonia. The presence of dystonia suggests more severe illness and poorer prognosis.

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A number of virological diseases have been associated with parkinsonian features such as encephalitis lethargica, Japanese encephalitis (JE), western equine encephalitis, central European tick borne encephalitis, polio, Cocksackie B, measles, and varicella zoster.^{1–4} Of these JE is the most important as it is the commonest human endemic encephalitis affecting 50 000 people annually in South East Asia.⁵ In our earlier study of movement disorders in JE, we reported a variety of movement disorders which include hypokinesia, tremor, rigidity, and dystonia.⁴ The clinicoradiological and prognostic differences in the patients with parkinsonian features only and those with additional dystonia and dyskinesia have not been reported. In the present study, we compare the clinical, radiological, and prognostic features in patients with JE with parkinsonian features only and those having parkinsonian features with other movement disorders.

PATIENTS AND METHODS

During 1992 and 1998 we have managed 50 patients with JE and 35 of them had movement disorders. The diagnosis of JE was based on the following criteria:

Essential criteria—Patients presenting with acute encephalitic syndrome characterised by fever and altered sensorium in which malaria and septic meningitis have been excluded.

Supportive criteria—Patients (1) coming from JE endemic area; (2) with thalamic involvement on computed tomography

or magnetic resonance imaging (MRI); or (3) with a fourfold rise of IgG antibodies against JE virus by haemagglutination inhibition test, a positive mercaptoethanol test, Mac-ELISA, or virus isolation in the cerebrospinal fluid.

The patients fulfilling the essential and at least two supportive criteria have been included in this study.

A detailed neurological examination was carried out in all the patients. The level of consciousness was assessed by the Glasgow coma scale. Depending on the consciousness level, the patients were tested by pinprick, touch, joint position, vibration, and cortical sensations. The extrapyramidal signs such as rigidity, dystonia, dyskinesia, and other abnormal movements were also noted. Once the patient was conscious, hypokinesia, masking of the face, hypophonia, rigidity, and tremor were graded on a 0–4 unified Parkinson's disease rating scale and dystonia by the dystonia rating scale.^{6,7} In both these scales 0 refers to normal, 1 to slight, 2 to moderate, 3 to severe, and 4 to marked symptoms.

Cranial computed tomography was carried out using a third generation scanner. Axial sections (10 mm) were obtained parallel to the orbitomeatal line. Cranial MRI was carried out

Abbreviations: JE, Japanese encephalitis; MRI, magnetic resonance imaging

Figure 1 Patient with JE from group II who had status dystonicus. This patient had severe axial and limb dystonia (reproduced with patient's permission).

on a 2T scanner operating at 1.5T (Magnetom, Siemens, Germany). T1 (500/15/3-TR in ms/TE in ms/excitations), proton density (2000–2500/15–20/1), and T2 (2000–2500/80–90/1) weighted spin echo sequences were obtained.

JE patients with movement disorders were classified into two groups:

Group I—Group I patients had features of parkinsonism characterised by rigidity, tremor, hypokinesia, hypophonia, masking of face, or loss of postural reflexes.

Group II—Group II patients had additional features such as dystonia, chorea, or myoclonus in various permutations and combinations.

The outcome was defined on the basis of the functional status after three months into poor recovery if the patient was bedridden, partial if the patient needed help for daily living activities, and complete recovery if independent.⁶ The clinical severity, radiological changes, and outcome of both these groups were compared by the χ^2 test. The role of cerebrospinal fluid and the extent of MRI changes in predicting the outcome at three months for JE patients were also evaluated by χ^2 test. The severity of movement disorders and their recovery at the end of three months in both the groups were compared by two way analysis of variance followed by the *t* test.

RESULTS

During 1992 and 1998 we have managed 50 patients with JE; 35 of them developed various types of movement disorders. All the patients fulfilled the diagnostic criteria of JE. The patients' ages ranged from 2 to 64 years (mean 23.4) and 11 were females. During the acute encephalitic stage, Glasgow coma scale score ranged from 4 to 13 (mean 6.9). Seizures were reported in 13 patients during the acute stage of illness.

Group I

There were 16 patients in group I who had varying degrees of parkinsonian features. The parkinsonian symptoms appeared 1–4 weeks after the onset of illness as consciousness started improving and assessment was done once the patient was fully conscious. Mild rigidity was present in all (grade 1–2) and tremors in five. Mild to moderate tremors were present in the upper limbs in all and in tongue and perioral region in one patient. Hypokinesia was severe in 10 patients (grade 4) and moderate (grade 2–3) in three patients. Hypophonia was present in all the patients and was severe in 12 and moderate in four patients. Masking of the face was present in all except two patients and was marked in six patients. Pronounced loss of postural reflexes was noted in two patients. At three months of follow up, rigidity and tremor improved in all the patients. Hypokinesia improved by three grades in five patients, two grades in two patients, and one grade in two patients. In three patients hypokinesia improved from grade 4 to grade 0 after three months. Similarly hypophonia improved by three grades in six, two grades in two, and one grade in four patients. There was, however, no change in hypophonia in one

patient. Masking of the face was present in 14 patients, which improved in all except two. Postural instability improved by one month in one patient and by six months in the other. In this group cranial computed tomography was carried out in all and MRI in 15 patients. The computed tomogram was abnormal in six patients and revealed thalamic hypodense areas in all and hypodensity in basal ganglia, pons, and cerebral cortex in one patient each. Cranial MRI revealed more frequent changes and was abnormal in 13 patients. The MRI changes included thalamic involvement in 11, basal ganglia in four, midbrain in six, pons in two, cerebral cortex in four, and cerebellum in one patient. The MRI abnormalities were restricted to the thalamus only in four patients. At the end of three months, 10 patients had complete, two partial, and three poor functional recovery.

Group II

There were 19 patients in group II and their ages ranged from 7 to 64 years and seven were females. All the patients had marked rigidity: grade 4 in 10, grade 3 in six, grade 2 in two, and grade 1 in one patient. Tremor (grades 2–3) was present in eight patients which involved the upper limb in all and tongue and mouth in three patients. In one patient, tremor in the upper limbs appeared after three months. All the patients had grade 4 hypokinesia except one. On recovery from coma, all the patients were abulic and gradually started speaking in low volume monotonous speech. Masking of the face was present in all except one patient. These patients were distinguished by the presence of dystonia and choreoathetosis. Dystonia was mainly axial and fixed resulting in opisthotonus, retrocollis, or torticollis. Limb dystonia was present in six patients and jaw opening dystonia in two. Four of these patients developed markedly severe dystonia associated with severe painful spasms lasting for 5–30 minutes with a frequency up to 10–30 attacks daily (figs 1 and 2). There was severe exhaustion and dysautonomia such as hypertension, tachycardia, sweating, and fever. Choreoathetosis was present in two patients which regressed by four weeks.

Group II patients had less significant improvement at three months. Severe rigidity persisted in eight patients. Tremor however, improved in six out of eight patients: grade 4 hypokinesia, hypophonia, and masking of face persisted in six, seven, and two patients respectively. In the remaining patients, there was one to two grades of improvement. Axial dystonia improved completely in four and severe dystonia (grade 4) persisted in four patients. A two grade improvement in dystonia was present in three patients and one grade in five. At the three months of follow up, only four patients had complete functional recovery, seven partial, and eight poor recovery.

Computed tomography was carried out in 17 and MRI in 13 patients. Computed tomography was normal in eight and MRI normal in one patient. The distribution of lesions seen on computed tomography and MRI was similar to that found in

Figure 2 Cranial MRI, axial section, T2 sequence of the same patient showing hyperintense lesion in thalamus and basal ganglia bilaterally.

Table 1 Clinical and radiological features in patients with JE with movement disorders

Features	Group I (n=16)	Group II (n=19)
GCS mean (range)	6.6 (4–13)	7.2 (4–14)
Radiological		
CT/MRI numbers	6/15	17/13
Cortex	1/4	0/0
Thalamus	6/11	9/11
Basal ganglia	1/4	1/6
Midbrain	0/6	0/1
Pons	1/2	0/1
Cerebellum	0/1	0/0
Outcome		
Poor	3	8
Partial	2	7
Complete	10	4

CT, computed tomography; GCS, Glasgow coma scale score.

group I (see table 1). On MRI, thalamus only was involved in three patients and basal ganglia only and midbrain in one patient each.

The comparison of extrapyramidal features in groups I and II are shown in table 2. The initial scores of rigidity, hypokinesia, masking, and hypophonia were higher in group II compared with group I and showed less pronounced recovery. The occurrence of parkinsonian features only and parkinsonian features with dystonia was not related to the initial Glasgow coma scale score ($\chi^2=4.82$, $df=2$, NS) and was also

not related to the extent of radiological involvement seen on MRI, which was classified into thalamic involvement only and thalamic involvement with other areas ($\chi^2=2.30$, $df=2$, NS). Outcome of the patients at three months, however, correlated with the type of movement disorder ($\chi^2=6.23$, $df=2$, $p<0.05$). In group I, only three patients had a poor outcome whereas in group II, eight had a poor recovery. Similarly 10 patients in group I and only four in group II had complete recovery. Employing one way analysis of variance, followed by the *t* test, of the initial parkinsonian features, rigidity was more marked in group II ($p<0.01$) whereas hypokinesia, hypophonia, and masking were not significantly different. Comparing the residual parkinsonian features at the end of three months there was significantly higher scores for rigidity ($p<0.01$), hypokinesia, hypophonia, and masking of the face ($p<0.05$) in group II. These results are consistent with a more severe illness and higher level of disability in group II compared with group I. The three month outcome was not significantly related to cerebrospinal fluid abnormalities ($\chi^2=0.88$, $df=1$, NS) and extent of MRI changes ($\chi^2=0.88$, $df=2$, NS).

DISCUSSION

In the present study, 70% of patients with JE developed movement disorders in the acute or subacute stage of the illness. The movement disorders were noted 1–4 weeks after the onset of illness as the consciousness of the patients started improving. Parkinsonian features were the commonest and were present in all JE patients with movement disorders. The parkinsonian syndrome in JE patients was characterised by varying severity of rigidity, hypokinesia, hypophonia, and masking of the face. Tremor, however, was less frequent compared with other symptoms, and was present in 37% of patients only. Tremor was localised to hand, tongue, and perioral region and tended to improve in all except one patient by three months. Loss of postural reflex was noted in two patients and regressed by the first or sixth month respectively. Rigidity, hypokinesia, and masking of the face also regressed substantially but hypophonia was striking in most patients and was an important sequelae in the majority of JE patients. Laryngeal dysfunction leading to hypophonia is common in idiopathic parkinsonism and was reported in 89% of patients.⁹ In a recent study reduced thyroarytenoid muscle amplitude and low background contraction were noted in parkinsonian patients.¹⁰ The observed hypophonia in JE patients may be a manifestation of hypokinesia and bradykinesia of laryngeal muscles. The parkinsonian syndrome in JE differs from idiopathic Parkinson's disease because of the lower frequency of tremor and higher frequency and severity of hypophonia. Moreover, these patients tend to improve with time. A number of movement disorders may be superimposed on the parkinsonian syndrome in JE. These movement disorder include dystonia, chorea, and athetosis. Dystonia is the commonest of these movement disorders in JE and is characterised mainly by its axial distribution and fixed pattern. Thalamic dystonia has been reported to be fixed rather than

Table 2 Mean score of movement disorders in two groups of patients with JE; values are mean (SD)

Features	Group I		Group II	
	Initial	Final	Initial	Final
Dystonia	0	0	3.2 (0.92)	1.79 (1.61)
Rigidity	1.19 (0.54)*	0	3.32 (0.89)**	1.79 (1.84)
Hypokinesia	3.19 (1.42)**	1.25 (1.34)	3.95 (0.23)**	2.21 (1.51)
Hypophonia	3.44 (1.09)**	1.31 (1.30)	3.95 (0.23)**	2.37 (1.50)
Masking	2.50 (1.41)**	0.94 (1.44)	3.00 (1.15)**	1.84 (1.34)

* $p<0.05$, ** $p<0.01$ comparison between initial and final values of each group.

mobile.¹¹ Mouth open dystonia, orofacial dyskinesia, and tongue dystonia may also be present in JE. This results in various forms of disabling posture such as opisthotonus, torticollis, retrocollis, etc. Status dystonicus is a serious and life threatening complication and four of our patients had markedly severe dystonia associated with autonomic dysfunction and exhaustion. Dystonia regressed during the follow up period but at a slower rate compared with parkinsonian syndrome.

The pathophysiology of akinesia and various dyskinesia involves disruption of the motor-basal ganglia circuit. This circuit begins with cortical output to the striatum followed by projections from striatum to pallidum, pallidum to thalamus, and finally thalamus to cortex. Abnormal thalamic output to the frontal cortex, particularly to the supplementary motor cortex is responsible for dyskinesia and akinesia. Substantia nigra and subthalamic nucleus are also important parts of this circuit. Chemical or pathological changes in these nuclei lead to reduced thalamic output to the cortex resulting in parkinsonian syndrome.¹²⁻¹³ In our study, MRI revealed midbrain involvement in six out of 15 patients in group I and seven out of the 13 patients in group II; lentiform nuclei were involved in four and six patients in groups I and II respectively. These lesions could be responsible for the parkinsonian syndrome in these patients. There were, however, four patients in group I and three in group II who had only thalamic involvement on MRI. In these patients, thalamus or thalamocortical projections could be responsible for the parkinsonian features. These results are in sharp contrast to the meta-analysis of thalamic lesions in which no examples of isolated parkinsonian rigidity and dyskinesia with thalamic or subthalamic lesions were found.¹⁴ There were two patients in group I and one in group II who had a normal MRI. The presence of parkinsonian features in these patients could be due to functional alterations in the above mentioned circuit.

Focal central nervous system lesions affecting lentiform or caudate nuclei, particularly those disrupting the striatopallidothalamocortical pathway may cause dystonia.¹⁵ A study using positron emission tomography in hemidystonic patients with basal ganglia or thalamic lesions demonstrated metabolic overactivity in frontal association areas when moving the affected limb.¹⁶ Dystonia after thalamic stroke has been reported after 1–9 months of ictus.¹⁷ In our study, dystonia was noted in nearly half of our patients in the acute or subacute stage of JE. It was mainly fixed axial dystonia with or without limb involvement. Fixed and truncal dystonia was present in 16 out of 33 patients whose lesions were restricted to the thalamus.¹⁴ Severity of dystonia in our study also ranged between mild and severe. In our study, no specific radiological correlate for presence or severity of dystonia was found. However, two of the three JE patients with mouth open dystonia had midbrain involvement in addition to thalamic lesions. Blepharospasm or Meigs' syndrome has been reported with

brainstem lesions.¹⁸ In our study, the patients with only parkinsonian features had a better outcome compared with those with dystonia. This may suggest that group I patients may represent a less severe illness compared with group II.

It can be concluded from this study that JE can result in a transient form of parkinsonian features which is characterised by a lower frequency of tremor and prominent hypophonia. Presence of dystonia suggests a more severe illness and a poorer prognosis.

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